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The Bulletin *of the*
Association *for the* Study *of*

Internal Secretions

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Endocrinology

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January, 1922

A SPONTANEOUS ATTACK OF TETANY DURING A PAROXYSM OF HYPERPNOEA IN A PSYCHO-NEUROTIC PATIENT CONVALESCENT FROM EPIDEMIC ENCEPHALITIS.*

(One figure in text)

LEWELLYS F. BARKER, M.D. AND THOMAS P. SPRUNT, M.D.
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The patient, a young man 18 years of age, first came under our observation on February 4, 1921. The chief complaints were "hard breathing," "difficulty in sleeping," and "slipping spells" during which he loses control of himself for five or ten minutes and has only a faint recollection afterwards of what has happened. During the "spells" he talks a great deal, knows that he is talking excessively, but "has no control" over himself.

Family History: The father is living (age, 65) and in good health except for occasional indigestion. The mother is living (age, 51) and is very nervous and solicitous. The maternal grandmother is also very nervous. The parents have lost three children and the patient is the only surviving child. There is a history of tuberculosis in the mother's family. All of the attention, worry and solicitude of a very nervous mother have been concentrated upon the patient. He sleeps in her room at night and she occasionally arises "to see that he is safe." Any slight deviation from the routine, a late arrival at meals or remaining out a little late at night, throws the family into a panic.

* This case was reported in abstract at the meeting of the Association of American Physicians held in Atlantic City, N. J., in May, 1921.

Past History: The patient has always been somewhat nervous and rather dependent, especially in the home, but despite the possibilities suggested by the heredity and environment he has seemed to be a fairly healthy and vigorous boy, not of the studious type but fond of athletics and out-door sports.

There is a history of diphtheria, measles and tonsillitis. Two years ago a large abscess on the left side of the face was incised and healed satisfactorily. Three years ago he suffered a slight blow on the head in an automobile accident.

His digestion had always been good up to the time of the present illness.

There has been occasional nocturia, the patient being compelled to urinate once or twice during the night for years. When about 10 years of age, enuresis occurred practically every night for a year or more and then gradually improved. This recurred for a time during the present illness.

The patient drinks coffee once a day and smokes from 8 to 10 cigarettes each day. His work at school had been satisfactory. He had expected to enter the State University last year, but was prevented by illness.

Present Illness: The present illness began on the evening of January 24, 1920, with a severe headache and a chill. He was up and about the next day. On the day following, while the patient was playing volley ball at the Y. M. C. A., he became greatly excited, accusing another player of cheating. He carried his protestations to extremes and had to be removed from the gymnasium and carried home. For the 15 days following he was in a condition of acute mania, talking almost incessantly day and night, sitting up in bed and preaching excitedly about things that at that time were of interest in local politics. There was complaint of diplopia and there was fever during these two weeks, the temperature rising each day to about 102° F. The fever and the delirium gradually ceased but the patient did not recover rapidly. He remained in the house, most of the time in bed, and about 5 weeks after his first attack began to suffer from indigestion with much gas. This was accompanied, he says, by "something like asthmatic breathing," a very deep, regular and labored respiration occurring in irregular paroxysms. He took a great deal of soda and other medicines in the hope of relieving his indigestion. In June, an acute appendicitis developed, and at the operation a gangrenous appendix was found and removed.

Later, many pimples (acne) appeared on the face. A large abscess developed in the region of the left tonsil and was incised. In September, 1920, the tonsils and adenoids were removed.

During the spring of 1920 there were occasional "mental lapses" in which the patient would talk at random, quite incoherently. From July, 1920, until January, 1921, there were no such mental lapses, but 3 occurred during January; of these, 2 lasted for only a few

minutes, but one on the 12th of January lasted for about 3 hours. He realizes the approach of these "lapses." As he expresses it, he "feels himself slipping"; he becomes drowsy and weak. He still suffers a great deal from indigestion, constipation is marked and the dyspnoea persists. He describes also what he speaks of as "trembling spells," which occur daily.

He has a large appetite, complains frequently of hunger at night, and has consumed large quantities of milk in addition to his regular meals, so that he has gained about 25 pounds in weight during the past year.

He is very much more nervous than formerly, sleeps poorly, frequently lies in bed and worries about "impossible things." He occasionally walks in his sleep. There is some depression, but there have been no hallucinations nor delusions. He is not fearful nor suspicious and there have been no attacks of morbid anger.

Physical Examination: During the recording of the anamnesis there were periods of very deep and labored respiration, the accessory muscles of respiration being brought forcibly into play. The breathing was very deep and regular and did not interfere materially with speech. As a rule such periods lasted for from 2 to 3 minutes. At the beginning of the physical examination, possibly due to the mental diversion, this deep breathing ceased entirely.

The patient is 5 feet 8 inches tall and weighs 160 pounds stripped. He is approximately 5 pounds over his calculated ideal weight and looks rather larger above the waist than below. The posture is good, the spine straight and the movements of the spine are excellent. Station is good with eyes open and with eyes closed. The gait is normal.

The eyes are slightly prominent and the lid slits are a little wider than usual, the left lid slit being wider than the right. There is a slight Dalrymple sign, but von Graefe's sign is negative. The left pupil is a little larger than the right; both are round and react actively to light. The extraocular movements are good in all directions, but there is slight nystagmus in extreme lateral positions of the eyes. There is no diplopia at present.

The face is covered with pimples, there is a small boil on the left side of the chin, and a long scar (following the surgical incision) below the left jaw. There is no tenderness over any of the paranasal sinuses but there is slight nasal obstruction on the right side. Several molar teeth are missing. There are no obviously dead teeth. The gums are in fair condition. The tonsils have been cleanly removed. The throat is slightly reddened. The tongue is of normal size, slightly coated but not tremulous, protruded in the midline. The mucous membranes are of good color. There is no general glandular enlargement.

The thyroid isthmus is palpable but not full. The lateral lobes are not felt. There is slight swaying of the hands but no fine tre-

mor. The hands are well shaped, a little large; the lunulae of the nails show very distinctly.

Radial pulsations are synchronous, the rate 72; the pulse is regular in force and rhythm and of good volume. The radial wall is not thickened. Blood pressure 125/85. The examination of the heart and lungs is negative.

The abdomen shows the scar of a surgical incision over the right lower quadrant, but otherwise is natural in appearance. The walls are soft. There is no tenderness; there are no abnormal masses. Liver and spleen are not felt. There has been no hiccoughing.

The abdominal reflexes are very active, equally so on the two sides. There has been no history of muscular twitchings. Deep reflexes of the arms are equal on the two sides and moderately exaggerated. Knee kicks are slightly exaggerated. Babinski sign is negative. Feet are cold and moist, slightly cyanotic.

Muscular strength is good, and sensations of touch, pain, sense of position are unimpaired. There is no ataxia.

Ophthalmoscopic examination shows the discs sharply outlined and of good color. Physiological cupping is decidedly larger than usual. Vessels are of normal size and normally distributed.

The external genitalia are normal in appearance. There is a tight anal sphincter. The prostate is of normal size and not tender.

The axillary and pubic hairs are abundant, and normal in distribution except for a transverse rather than triangular crines. Trichosis elsewhere is about normal in amount.

During the latter half of the examination the paroxysms of deep, forced respiration recurred at intervals. With the increased excitement attendant upon the entrance of a consultant the respirations became deeper and more rapid and continued so. After several minutes there was marked sweating of the face and of the axillae and fibrillary twitching of the muscles of the left eyelid was observable. A few moments later, there was a typical acute attack of tetany (Fig. 1) with bilateral carpal spasm, which persisted for 15 or 20 minutes and then gradually passed off. It was accompanied by profuse sweating of the face and neck and by subjective numbness of the affected extremities. The feet were not involved. During the attack there was a Chvostek sign of first degree strongly positive on the right side, not quite so marked on the left. The spasm of the left hand and arm passed off a little earlier than that on the right side. A short while after the attack the Pool-Schlesinger leg test (holding the leg extended at the knee and in marked flexion at the hip) failed to bring on spasm of the foot.

NEUROLOGICAL EXAMINATION (Dr. H. M. Thomas).—The patient is a well nourished boy who gives a remarkably good history of his disease. Now and then during the interview he will take a number of deep breaths. At other times he will talk along with very slight

interruption. After the examination began the breathing became more labored.

The pulse beats regularly at about 80.

Ophthalmic examination showed: Right optic nerve,—temporal edge distinct; nasal edge also distinct; physiological cup deep and rather large; veins of normal size, not tortuous; arteries normal; retina not disturbed so far as seen. Left optic nerve,—edges distinct; physiological cup deep; veins and arteries normal.

The pupils are moderately dilated; they react to light, directly and consensually, and contract during accommodation. The visual apertures are about equal.

At times, particularly during deep inspiration, there is a tendency for the lids to droop. This is more marked on the right than on the left.

Fig. 1. Patient in spontaneous attack of tetany during a paroxysm of pathological hyperpnoea incident to convalescence from epidemic encephalitis (psychotic-ophthalmoplegic type).

The movements of the eyeballs are normal. In the extreme lateral positions there are some nystagmoid movements. Repeated movements (looking up 20 times) show not the slightest evidence of fatigue.

The muscles of mastication act well. The jaw jerks is active. Sensation on the face is normal.

Facial expression is good, except for a slight drooping of the eyes during a dyspneic attack. The facial muscles act well and symmetrically. Percussion of the branches of the facial nerve does not now produce any unusual muscular contraction.

Hearing is normal.

The soft palate and tongue act normally.

Blood pressure, systolic, ranges now between 115 and 120. When pressure of the cuff is maintained at over 200 for over a minute, there is no tendency to spasm.

There is no tremor of the hand. The thumb-finger test is done very rapidly. There is no ataxia; muscular strength is good; no muscular twitchings are noted.

The biceps and triceps reflexes are hyperactive.

The abdominal reflexes present and equal.

The knee-heel test is done well on both sides. Muscular strength is normal. No muscular twitchings are noted.

Knee jerks are present, slightly hyperactive. Ankle jerks are present, slightly hyperactive and equal; no clonus is obtained.

On plantar stimulation there is practically no response. What there is, shows that the great toe moves in plantar flexion. This is also true on descending tibial and sub-malleolar stimulation.

No objective sensory disturbance is discovered.

Electrical Examination: Right ulnar nerve, stimulated above elbow, gives cathode closure contraction at 1½ milliamperes; anodal opening at 1½; anodal closure at 3; cathodal opening not obtained at 5, nor is there a sustained tetanus with cathodal closure. Cathodal opening contraction is not obtained with any strength of stimulus.

Comment: The patient gives an interesting history of what must have been encephalitis, and I am inclined to regard his deep breathing, which is very like some cases of what I have taken to be hysterical breathing, as a functional hang-over from the infection. He is the only child remaining and his mother has evidently watched him with great anxiety. The curious attacks that he has, which suggest *petit mal*, may be an evidence of anatomical change. I was entirely unable to get any evidence of tetany, and a loss of consciousness in tetany is certainly unusual, except in attacks of extreme severity.

PSYCHIATRIC EXAMINATION (Dr. Richards): The patient's mental picture during the onset of the acute illness in January, 1920, seems to have been a frank delirium. Following this, he was in bed most of the time for two months in a rather dull, inert condition. During this time he had no special complaints except those of gas, distention and the sighing reaction which he now shows. He thinks the gastrointestinal symptoms have been improved since his appendectomy in June, 1920. Just now he complains of a vague nervous state in which he is easily upset by trifles and sometimes has trembling and jerking attacks. During the daytime he is much less alert than at night. He says that he has been too wide awake to sleep before 1 a. m. Aside from the above statement of mental attitude, the psychiatric examination revealed nothing of importance.

He responds to the sensorium tests correctly and without retardation. The patient has no association connected with the sighing re-

action which apparently developed during the acute illness. While concentrating during the examination he went for five or ten minutes without this symptom.

The present picture is suggestive of post-encephalitic phenomena arising in a suggestible makeup. There is apparently a good deal of petting and coddling on the part of the parents.

EAR, NOSE AND THROAT EXAMINATION (Dr. H. R. Slack).—*Sinuses:* There is no tenderness on pressure over the sinuses or mastoids. On illumination the frontals are very large and clear; both antra are clear.

There is no enlargement of the lymph nodes at the angles of the jaw.

Nose: There is good breathing space on both sides of the nose. There are no polypi; no pus visible.

Teeth are in good condition.

Tonsils have been removed; some remnants remain on both sides, but they are not apparently infected. The *nasopharynx* is negative.

Larynx: The epiglottis is turban-shaped, of the infantile type; the vocal chords are slightly reddened and move normally.

The *ears* are normal.

Impression: There is no focus of infection in the nose, throat or ears.

LABORATORY REPORTS.—*Report on basal metabolism:* Height in centimeters, 175; weight in kilograms, 71.8; body surface in square meters, 1.87; CO_2 eliminated per square meter per hour in grams, first period 10.32, second period 11.59. The examination was made twice on account of the deep breathing which washed out the CO_2 before the test. Both tests he took comfortably. The first test was 22.5 per cent below the expected for the patient's age and sex, and the second was 12.9 per cent below. It is felt that the metabolism would be normal or a little low, were it possible to avoid the deep breathing. The second test was taken very soon after the first and when deep breathing was not present.

Blood examination showed: R. B. C., 4,800,000; hemoglobin, 88%; W. B. C., 5,000; P. M. N., 65%; P. M. E., 0; S. M., 25; L. M., 10. The blood smear was normal in appearance.

The blood Wassermann reaction was negative.

The non-protein nitrogen of the blood was 27.2 milligrams per 100 c.c.

Gastric analysis: After an Ewald test breakfast, 50 c.c. were recovered, the contents having a normal gross appearance. There was some mucus present. Free HCl was 50 acidity per cent; total acid, 58 acidity per cent. Tests for occult blood and lactic acid were negative Microscopically there were many yeast cells, a small amount of starch, but no sarcinae nor Oppler-Boas bacilli.

Examination of the *feces* was negative.

Urine: Reaction was acid; specific gravity, 1018-1008. There was a faint persistent trace of albumin in both day and night specimens. No sugar, no acetone, no indican were found. Miscroscopically, there were occasional epithelial cells, but no red cells nor casts. Phenolsulphonephthalein test showed: first hour, 35%; second hour, 23%; total for the two hours, 58%.

Cerebrospinal fluid findings were: Fluid clear; 3 cells; globulin negative; Wassermann negative.

ROENTGENOSCOPIC REPORTS: The lungs and heart are negative. The diaphramatic excursions are satisfactory. The retrocardiac space is clear.

Fourteen hours after a barium meal there is a thin, wafer-like shadow of retained barium near the pyloric end of the stomach. The barium meal fills the colon as far as the splenic flexure; beyond this point the colon is indicated only by its gaseous content. The colon is in good position. There is some caecal stasis.

At the second barium meal swallowing is normal. The stomach is of the cow-horn type, filled without obvious defect; the pylorus lies across the spine and is drawn slightly downward. The tonus and mobility of the stomach are good. The pylorus is fairly movable.

ROENTGENOGRAPHIC REPORTS. — *Gastrointestinal tract:* The stomach is of the cow-horn type, sluggish in appearance, showing very little peristalsis; the pyloric end of the stomach is blunt and there is no more than a suggestion of a duodenal cap. There is a little barium remaining in the stomach 14 hours after the first meal. In this series, however, the stomach is empty 5 hours after the second meal. There are no definite filling defects noted in the stomach. The colon is in good position. There is moderate stasis in the caecum, ascending colon and hepatic flexure. There is no significant ileal stasis. There is a good deal of gas in the colon.

Dr. F. H. Baetjer, on examining this series, suspected, however, the existence of an old pyloric ulcer.

Lateral skull: The sella turcica is smaller than the average and almost closed in. The bony outlines are apparently normal. The sphenoidal and frontal sinuses are clear. The tables of the skull are not remarkable.

Paranasal sinuses: Frontals and ethmoids are clear; both antra are slightly cloudy, the right more than the left, suggesting an old infection.

REARRANGEMENT OF DATA

Young man, aged 18.

Chief complaints: Hard breathing; insomnia; slipping spells; nervousness.

Habits: 8 to 10 cigarettes a day.

Infections: Tonsillitis; diphtheria; an abscess on the face; appendicitis.

Operations: Appendectomy; tonsillectomy; incision of abscess.

Respiratory system: X-ray of sinuses shows a slightly cloudy right antrum, evidence of an old infection; special nose and throat examination is negative. The lungs are negative. There are periods of deep and slightly accelerated breathing, especially on any excitement.

Circulatory system: Occasional dyspnoea. Pulse rate, 72. Blood pressure 125/85. Heart, normal.

Blood and hematopoietic system: R. B. C., 4,800,000; hemoglobin, 88; W. B. C., 5,000; Wassermann reaction, negative; polymorphonuclear neutrophils, 65%; eosinophils, 0; small mononuclears, 25%.

Digestive system: Free hydrochloric acid, 50 acidity per cent; total acid, 58 acidity per cent. No occult blood. Stool, normal. No digestive symptoms until present illness. Since then a gangrenous appendix; operation with drainage; constipation, gas, occasional pain in left side; physical examination of abdomen now negative. X-rays: 14-hour gastric retention, but in this series no 5-hour retention after second meal; caecal stasis; possibility of an old pyloric ulcer. Teeth in good condition.

Urogenital system: Urine: Specific gravity varies from 1008 to 1018. A faint trace of albumin. No sugar, no casts nor other abnormal elements. External genitalia normal. Phthalein excretion, 58% in two hours. Non-protein nitrogen of the blood, 27.2 mg. per cent.

Locomotor system: Negative.

Nervous system and sense organs: Always nervous. Only child of solicitous parents. Acute illness in January, 1920, with fever, diplopia and maniacal delirium for two weeks. Residuals: Increased nervousness, periods of very deep breathing, lethargy during the day and nervousness and insomnia at night, trembling spells, occasional lapses into slightly manic state with partial amnesia. Neurological examination negative for signs of organic disease; possibility of residual *petit mal* attacks. Psychiatric examination: suggests post-encephalitic phenomena in a person of suggestible makeup. Cerebrospinal fluid normal.

Metabolism and endocrine system: Slightly overweight (five pounds). There was a gain of about twenty-five pounds with the present illness. Looks large above the waist. There are slight hyperthyroid eye signs. Hands rather large. Sella turcica small and nearly closed in. The basal metabolism was difficult to determine owing to the deep breathing. The figures read low, but it was supposed that the metabolism would prove normal or a little low if the deep breathing could be avoided.

Remarks: There was a typical attack of tetany with bilateral carpal spasm while under observation, apparently resulting from prolonged hyperpnoea. Later, during the course of the study, there was no increased electrical excitability of the motor nerves and no evidence of latent tetany could be discovered.

DIAGNOSTIC SUMMARY

1. Post-encephalitic state, with *petit mal* attacks, functional paroxysmal hyperpnoea and a single spontaneous attack of tetany.
2. Right-sided abdominal adhesions with caecal stasis, constipation and gastric hyperacidity; suspect pylorus.
3. A mild endocrinopathy.

THERAPEUTIC SUMMARY

The therapy advised in this case included:

1. A thorough rest and upbuilding treatment with isolation away from home and family, with occupational therapy and psychotherapy.
2. A change in the diet with diminution in the amount of carbohydrates and especially of milk, which the patient had been drinking in large amounts. The diet recommended included emphasis upon fruits and green vegetables, and moderate amounts of meat, with smaller amounts of easily digested carbohydrates and fats.
3. For the caecal stasis and constipation mineral oil, one ounce at night and one-half an ounce in the morning. During the period of observation of ten days the bowel functions were apparently very satisfactorily regulated by the use of mineral oil alone. The patient had been in the habit of taking cascara every night and frequently compound cathartic pills in addition.
4. The gastric hyperacidity was to be combatted by means of an antacid powder after meals.
5. The right side of the abdomen and the nervous system were to be kept under close observation.

The patient did not remain long under our direct observation, but went home after a period of about ten days, taking our report to his home physician. He had been assured that the hyperpnoea was, in our opinion, of functional origin and that it would disappear. He was rather anxious to go home and was kept in a state of suspense for three or four days before this decision was made. His hyperpnoea would occur on any slight excitement during our observation of the case, but never to the extent present at the first examination.

A letter from the patient four or five days after his departure stated that he had not been troubled a single time with his breathing since his return home and that he was feeling fine. This was corroborated a few days later by a letter from his father, who wrote that he had been entirely free from the labored breathing and was more nearly normal than he had been since January, 1920. He came under our observation again several months later. His condition had continued to be fairly satisfactory until June, when there was a return of the insomnia and restlessness at night with increased nervousness and depression. When especially nervous and afflicted with the hyperpnoea he had at times experienced some numbness and a feeling of stiffness in the hands, but there had occurred no outspoken attack of tetany. During a period of rest and upbuilding, with complete isolation, he

soon became comfortable and entirely free from symptoms. On resuming a more natural life there were some neurotic manifestations, but the nervous state in general showed great improvement.

DISCUSSION

This case presents a number of interesting features. It adds another to the already long list of cases of epidemic encephalitis in which maniacal symptoms predominate at the onset. It illustrates, too, a point which has been previously noted, that patients with a psychopathic trend and environment are apt to show marked psychoneurotic residues after an attack of encephalitis. The rapid improvement, also, after a brief period away from home and strong reassurance, was striking and encouraging.

The feature that interested us particularly, however, was the occurrence of an acute attack of tetany during our first examination. The cause of this attack of tetany seemed fairly obvious, but would have been difficult to understand had it not been for the recent experimental physiological studies of Collip and Backus and of Grant and Goldman. These observers showed that tetany regularly occurs as a feature of voluntary prolonged hyperpnoea, probably as a result of disturbed acid-base equilibrium in the body. The observations of the experimentally-produced tetany were made apparently quite independently in the two laboratories, and somewhat similar observations have been recorded by previous workers who did not, however, recognize their significance.

Having the tetany particularly in mind, Grant and Goldman conducted a series of about twenty experiments and were able to produce tetany in each instance after the deep breathing at the rate of about twelve per minute had been continued for from thirteen to seventeen minutes. Their experiments were carefully controlled on the chemical side and the tetany was found to occur after decided changes had taken place in the alveolar air, in the blood and in the urine. The alveolar carbon dioxide tension fell, the blood became slightly more alkaline, the urine became decidedly alkaline, the plasma bicarbonate was reduced, the ammonia excretion was diminished, and there was a slight increase in the calcium content of the blood.

One of their experiments might be detailed as follows: After ten minutes of the deep breathing there was slight headache; after

thirteen minutes tingling in the hands; after sixteen minutes a positive Trousseau sign and a slight Chvostek sign; after seventeen minutes both hands tingled markedly; at twenty minutes a spasm of both hands; at twenty-three minutes spasm of the feet; there was no facial spasm. Twenty-one minutes after the beginning of the experiment the alveolar carbon dioxide tension was 20 mm., having been 40 mm. at the beginning of the experiment. At twenty-two minutes after the onset of the breathing the blood pH. was equal to 7.5 instead of 7.4, as it was at the beginning of the experiment. The plasma bicarbonate was 45.85%, having been 63.6% at the beginning of the experiment. The urine collected twenty-five minutes after the onset of the hyperpnoea showed a pH. 7.9, a change from 4.9 before the hyperpnoea

The subjects of these experiments were presumably normal men who showed no evidences of latent tetany. The physiologists controlled their experiments to show that food had no influence. Further, they proved that deep breathing itself had no effect, provided the carbon dioxide tension of the alveolar air was not lowered; this they controlled by rebreathing carbon dioxide. Their explanation of the chemical changes is that the deep breathing washes out the carbon dioxide from the alveolar air, reduces the blood carbon dioxide and disturbs the ratio between the carbonic acid and the sodium bicarbonate on which the hydrogen-ion concentration of the blood depends. On re-establishing this ratio the sodium bicarbonate passes out of the blood plasma into the tissues and a considerable portion also is excreted by way of the kidneys. Apparently the carbon dioxide can be washed out more rapidly than the sodium bicarbonate is decreased by excretion or otherwise. Consequently a relative alkalosis develops and at the same time there is a reduction of the alkaline reserve due to elimination of the sodium bicarbonate from the body fluid in the effort to maintain constant hydrogen-ion concentration.

Disturbances of acid base equilibrium toward the alkaline side have been noted before in the study of tetany. Wilson, Stearns and Thurlow and Wilson, Stearns and Janney have noted in parathyroidectomized dogs a period of alkalosis just before attacks of tetany occur. They found that the injection of acid or of calcium salts relieved the tetany. They attribute part of the beneficial action of the calcium salts to a relative increase in the acid radicals by this means, the formation of calcium phosphate $Ca_3 (Po_4)_2$ from the carbonate, thus liberating hydrochloric acid. Further, Howland and Marriott reported three cases of tetany occurring in infants after the administration of sodium bicarbonate. Harrop reported such a case in an adult

after the administration of sixty grams of sodium bicarbonate. Ammonia poisoning also produces similar symptoms.

In previous studies upon tetany it has been found that the calcium of the blood is uniformly low and it has been considered that the administration of calcium therapeutically replaced the needed calcium and in this way protected the body from tetany. In these physiological experiments in which tetany was produced by hyperpnoea it has been found on the other hand that the calcium of the blood is slightly increased rather than diminished. The question was raised, however, by the authors, as to whether this calcium were in available form.

The case reported in this paper is, in our opinion, an example of tetany brought about as an acute manifestation of the chemical changes in the body incident to hyperpnoea. There is no evidence whatever that the patient suffered from chronic or latent tetany. There had been no previous attack and no history suggesting tetany in his infancy or early youth. A half an hour before the attack occurred, during an interval between periods of deep breathing, there were no evidences of latent tetany—a negative Trousseau, Chvostek, etc. A day or two following this attack there was no electrical hyperexcitability of the peripheral nerves demonstrable. This case, as far as we know, is the first one in the literature illustrating the occurrence of tetany as a complication of a hyperpnoea that is the result of disease. Dr. Fritz Gundrum of California reports by personal communication that he has seen a similar case recently.

There has been a decided tendency in recent years to unify our ideas as to the etiology of tetany and to ascribe the most importance to defective functioning of the parathyroid glands. It is difficult to bring the hyperpnoea experiments of the physiologists and cases like that here reported into relationship with parathyroid deficiency. It seems possible that parathyroid deficiency may ultimately bring about a disturbance of acid-base equilibrium in the body and hence produce tetany, and that hyperpnoea brings this same condition about much more quickly and without the intervention of the parathyroids. Or it may be that tetany is a symptom complex, due not to any single etiological factor but to any condition which heightens the irritability of the peripheral nerves. Certainly, it has been definitely demonstrated that this disturbance of the acid-base equilibrium

causes a very marked increase in the irritability of the peripheral nerves so that tetany can be very readily produced even in otherwise normal individuals.

Active therapeutic measures directed toward the tetany were not necessary in this particular case. When the patient was left with one companion in the room and his excitement quieted down the deep breathing stopped and the tetany disappeared. A few moments later the Pool-Schlesinger leg test showed no tendency to spasm on the part of the feet or leg muscles. Unfortunately, material could not be collected at the time of the attack of tetany for chemical studies.

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HYPOPITUITARISM AND ITS TREATMENT*

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INTRODUCTION

Clinical use of the term hypopituitarism implies recognition of disease pictures dependent primarily at least upon insufficient pituitary secretion. It is certainly convenient both from a diagnostic standpoint and as a basis for therapy to conceive of the hormonic disorders of the pituitary as resulting from either an excessive secretion of normal pituitary products or a diminished production of normal hormones. Whether or not this will prove to be scientifically accurate remains for future proof. It is quite conceivable and indeed rather likely that the simple conception of a quantitatively increased or decreased amount of normal hormones will not be the final explanation of the varied and complex clinical pictures that are at present ascribed to pituitary disease. It may well be that these pictures are produced by a changed or what may be termed abnormal secretion and that therefore a more conservative and correct term for these disorders would be dyspituitarism. Accepting for the present the quantitative idea of hypo- and hyper-pituitarism the clinical manifestations in a given case necessarily depend on: first, the exact amount of normal secretion lacking or in excess; second, that time in the life-cycle of the patient when this excess or lack originated; and third, the sex of the individual. When chemical investigations will have revealed the actual hormone or hormones of the pituitary and when methods will have been devised that permit of their quantitative estimation in a given individual, then, obviously, a condition will arise where it would be possible to substantiate that an increased or decreased amount of such hormone or hormones will produce this or that clinical complex. On the other hand, if dyspituitarism is found to be the correct expression for pituitary disorders, such chemical hormones will

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not be recovered in their normal formulas but will be found as chemically altered products.

The problem, however, is not even as relatively simple as above presented because other complex factors must be added relating to the bilobar, or maybe even trilobar, constitution of the pituitary; that is to say, a clinical syndrome will depend not only upon the age of onset, the sex and the quantitative question of hypo- or hyper-pituitary secretion but also upon whether this is the result of deficiency or excessive secretion of the anterior lobe alone, the posterior lobe alone, or both lobes together or of increase in one and diminution in the other.. Before our clinical analyses can be accurate and our therapy precise and appropriate we must be certain as to just what abnormalities result from anterior lobe disease and what from posterior lobe involvement, and perhaps even from pars intermedia. Much investigation and information has accrued, most interesting and plausible, but surely no good can come of any pretense at this time that our knowledge in regard to these matters is in any sense complete or reliable.

We are accustomed to obtain some satisfaction in our clinical diagnoses of pituitary disorders from skigrams of the skull showing either enlarged or abnormally small sella turcica, but it should not follow that a normal sized sella rules out pituitary disease; nor does it follow that increased secretion necessitates an enlarged gland nor diminished secretion an anatomically small gland. Functional excess or insufficiency can result from a gland of any size whether large, normal, or small. We are all acquainted with instances of unmistakable hyperthyroidism in which goitre in the sense of an enlarged thyroid does not exist. The degree of toxicity in a case of Graves' disease is not related to the size of the thyroid gland. And precisely as the pathological changes in exophthalmic goitre or adenoma can not be correlated with the clinical toxicity or basal metabolism, so likewise the type of pituitary alteration is no index of the hormonic manifestations. It need only be mentioned that a tumor of the pituitary may produce either typical acromegaly or Fröhlich's dystrophy adiposo-genitalis.

The various clinical pictures ascribed to hypopituitarism have received their proof of pituitary origin from the finding of

pituitary disease at autopsy, from experimental partial hypophysectomies, and to a slight degree, from amelioration of signs and symptoms through specific pitiuitary substitution therapy.

THE HORMONIC MANIFESTATIONS OF HYPOPITUITARISM

The Osseous System: Insufficient pituitary secretion produces extraordinary abnormalities in many different portions and systems of the body and as before stated will produce quite different pictures depending upon whether the insufficiency arises in a pre- or post-adolescent stage. In fact, such insufficiency may have its origin prior to birth and it would seem even in the very earliest embryonic state. The osseous system is definitely involved in many cases of hypopituitarism, though perhaps not as strikingly as in the hyper-syndromes, such as gigantism and acromegaly. Certain types of dwarfism therefore may have their origin in insufficient pituitary secretion prior to adolescence and indeed the opposite of acromegaly, namely, acromikria, is sometimes noted, where the end of the nose and the chin and the fingers and toes are pointed instead of blunt. These small, markedly tapering fingers are quite suggestive.

The Subcutaneous Tissue: The subcutaneous tissues are very strikingly involved oftentimes and in quite differing manner—that is to say, one may have extreme emaciation as has been sometimes noted both in diabetes insipidus and in almost complete absence of the anterior lobe; or on the contrary extraordinary obesity which would seem to have a characteristic distribution. It would seem that pituitary obesity is predominately girdle obesity, the fat being astonishingly concentrated on the hips, the lower abdomen, and the mons veneris. The neck and shoulders, upper back and the nuchal region, chest, arms and legs for the most part escape this adiposity.

The Skin: The skin in hypopituitarism presents interesting changes. It is quite unlike the hypothyroid or myxedematous. It may be somewhat thick, though often it is thin, but it is not rough nor scaly. It is dry and smooth, as a rule, sometimes like the skin of a baby or child. Often it is marble-like in feeling and appearance, rather pale and waxy, and inelastic and lifeless. It is usually quite sensitive to slight trauma, such patients bruising very readily. When questioned they will admit that they frequently discover black-and-blue marks and do not remember any bump that could have caused them. Slight pressure from the thumb on the arm may cause such a discoloration. These patients rarely perspire and one of the first things that they become aware of soon after pituitary therapy is begun, is a new vitality, elasticity, and warmth of the skin. Some authors have remarked upon and indeed published photographs of a type of skin which is very finely wrinkled, dry and somewhat resembling parchment, but I am more inclined to the notion that this type of skin does not originate from pituitary lack but rather from gonadal deficiency. Possibly it may occur in both conditions since these are so frequently interrelated and difficult to separate.

The Hair and Nails: The quantity and distribution of the hair is oftentimes markedly altered in hypopituitarism. If the condition arises prior to adolescence, axillary and pubic hair is apt to be scanty, moreover in men the beard and mustache do not develop or only slightly, so that such patients never or very rarely shave. The pubic hair often assumes the characteristics of the opposite sex, that is to say, the male will not have any hair between the symphysis and the umbilicus, the base of the triangle being upward instead of the apex growing up toward the navel; vice versa in the case of the female, with some hair on the upper lip and chin and perhaps on the chest between the breasts, although this hypertrichosis in the female may be due to suprarenal disease. Trophic disturbances may occur in the nails with longitudinal or horizontal ridging termed onychauxis. A typical case of this sort (with photographs) was recently published by Hollander. I have seen this condition very remarkably exemplified in one case where the origin, however, would seem to have been atrophy of the testicles, rather than hypopituitarism.

The Generative System: Among the most important disturbances associated with preadolescent hypopituitarism must be mentioned those affecting the external and internal genitalia and the secondary sex characters. In the female the external genitalia remain quite infantile, while the internal organs are either exceedingly small and rudimentary or almost entirely undeveloped. (One patient, whose photograph is shown (Fig. 2), is 45 years of age and has never menstruated. No definite uterus can be palpated though a thickened strand of tissue in the broad ligament may represent such a uterine body.) If the hypopituitarism begins after adolescence, the appearance of the external genitalia will be normal, but the uterus is apt to atrophy, menstruation becoming irregular, several periods in succession being omitted, or actual amenorrhoea develop. The pubic hair may assume a masculine type and the voice may alter to a lower, harsher, masculine tone. Sexual frigidity is likewise apt to occur. When hypopituitarism affects the male prior to adolescence, the penis, testicles, and scrotum remain quite small and infantile like those of a boy of six years. Moreover, the scrotum may hang in deep folds around the base of the penis resembling somewhat the female labia majora. The pubic hair will be scanty or not present at all and if present will show feminine distribution. The voice may remain that of a boy even after adolescence, high-pitched and effeminate. The configuration of the body is often remarkably feminine, the breasts being considerably enlarged, the hips and the curves of the thighs having a shapely female contour, and the mons veneris being quite prominent. Such men may have but little sexual craving, and may progress to actual impotency. The internal genitalia of the male, the prostate and seminal vesicles, have curiously enough attracted little notice. I have attempted to go over the literature somewhat carefully for notes recording the condition of these organs, but with the exception of one instance in which mention was

made that the prostate was small, this phase of genital development appears to have been entirely overlooked. This would seem an extraordinary omission in view of the striking genital hypoplasia consistently recorded. In a recent number of the New York Medical Journal I called attention to this fact and reported briefly the cases of five boys, each one an excellent example of preadolescent hypopituitarism, in three of whom no prostatic tissue whatever could be palpated, and in the other two only an exceedingly diminutive organ. Since this note was made, two more cases have revealed the same condition. This would seem to suggest that the normal development of the prostate depends in part at least upon normal pituitary secretion.

The Metabolism. Metabolism is disturbed at times in pituitary disease as evidenced by polyuria and polydypsia, exemplified in striking fashion by diabetes insipidus. Whether or not this condition is always due to pituitary diesase is not yet finally established, and if due to pituitary involvement whether resulting from posterior lobe deficiency or pars intermedia is not yet clear. The fact that spectacular relief, even though temporary, results from administration of posterior lobe extracts does not positively prove its pituitary origin. Such argument would be as faulty as insisting that asthma is due to suprarenal disease merely because administration of adrenalin produces immediate temporary relief. Glycosuria and, on the other hand, greatly increased carbohydrate tolerance, is also found not infrequently in pituitary disease. Basal metabolism is predominantly under the control of the thyroid gland and great increase or decrease is usually attributable to disease of that organ. Whether or not the pituitary gland can also derange basal metabolism has not been finally settled, although the findings of some authors notably Tierney and Engelbach suggest that it may occasionally do so. At present most authorities ascribe the metabolic disturbances mentioned above and also adiposity to posterior lobe disease, but it hardly seems to me that this contention has been finally proven. The administration of posterior lobe in large doses by mouth and also hypodermically has not conditioned reduction in weight to any appreciable degree in some of my cases in which the obesity seemed characteristically of the pituitary type. That the anterior lobe may influence metabolism is suggested by the case reported by Roblee a few years ago in which administration of anterior lobe alone resulted gradually in a loss of over fifty pounds.

The Muscular System: The muscular system is also influenced by disordered pituitary function. In the earlier stages of gigantism and acromegaly there is often increased strength, endurance and muscular power. Later when hypopituitarism sets in and also in most cases of primary hypopituitarism, muscular weakness and fatigueability are quite marked. Whether this asthenia involving the muscular system and the blood pressure depend upon a secondary involvement of the suprarenals or whether it be purely of pituitary origin is not yet clear.

Miscellaneous: Pituitary disease exercises some influence perhaps upon the body temperature, the pulse rate and the blood pressure. In hypopituitarism the temperature is frequently continuously and considerably subnormal. The pulse rate may be quite slow and the blood pressure lower than normal. Hypotension has been frequently mentioned as a characteristic sign of hypopituitarism. I have found it so occasionally, but by no means as frequently as I was led to anticipate from the reports in the literature.

Mental and Emotional Disturbances: Finally, it is to be noted that pituitary disease involves the nervous system and more especially the psyche. It is exceedingly rash and unwise to leap into the domain of endocrinology for explanation of most mental and emotional derangements, but that some relation exists in some instances can hardly be denied. We are all familiar with the high-strung, agitated, frightfully nervous, anxious temperament of the sufferer from Graves' disease. We are likewise familiar with the stupid, listless, dull, apathy and indifference of the patient suffering from myxedema. We are also aware of the profound changes that occur in the male after castration —both in man and in animals—loss of virility, and energy, of agressiveness, of masculine love of combat. It is reasonable to associate guardedly some peculiar psychical states with pituitary disease when manifested by patients showing other unmistakable evidence of hypophyseal involvement. Tucker, especially, has called attention to what he terms the several pituitary psychoses. It seems probable that occasionally the pituitary may have an etiological role in epilepsy. The complete and amazing relief from epileptic attacks in some instances by administration of pituitary extract warrants such an assumption. The sweeping conclusion, however, attributing a pituitary origin to every case of epilepsy would be quite ridiculous. One hesitates to go so far as to associate mentality with the condition of the pituitary and yet it seems more than coincidental that marked mental retardation is so frequently seen in preadolescent hypopituitarism. Possibly the same cause that produces the hypopituitarism may be responsible for the mental retardation. Binet-Simon tests in many of these children reveal a mental age from three to eight or more years below their actual age and a few instances have been reported in which administration of pituitary to such children over a long period of time has markedly advanced their mental age and in a manner and at a rate which psychiatrists agree would not have occurred under ordinary circumstances. These results can not be finally accepted as yet, but they are at least encouraging and deserve careful scrutiny.

The above alterations in body function and body structure include fairly well the majority of the hormonic disturbances due to pituitary disease. Just which of these signs and symptoms should be ascribed to the anterior lobe and which to the posterior lobe cannot be positively stated at the present time. Some valuable and interesting classifications have been made, notably the recent one of Engelbach. In a gen-

eral way those disturbances that involve the osseous and the genital systems are believed to be of anterior lobe origin, while the disturbances of metabolism depend upon posterior lobe disease. These matters are, however, not definitely settled and, although they form interesting points for discussion, they should be accepted with some circumspection. Cushing, for instance, at one time at least, ascribed the genital disturbances to posterior lobe involvement. Obviously these points are of more than theoretic and academic interest, since the therapy to achieve desired results must be accurate and for this to be possible the precise functions of the three lobes must be clearly understood.

THE SEVERAL TYPES OF HYPOPITUITARISM

Illustrated by case reports and photographs

The signs and symptoms of hypopituitarism just described group themselves most frequently into a few readily recognized syndromes, as follows:

1. The Levi-Lorain type of pituitary infantilism.

2. The well-known Fröhlich type of dystrophia adiposogenitalis.

3. The less frequently recognized Neurath-Cushing variety.

Briefly, the Lorain picture is that of skeletal *under*growth with genital aplasia but *without* adiposity; the Froelich, skeletal *under*growth with genital aplasia *and* adiposity; Neurath-Cushing, skeletal *over*growth with genital aplasia and adiposity. It will be easier perhaps to visualize these clinical pictures by describing and figuring some typical cases.

CASE I. LEVI-LORAIN HYPOPITUITARISM

W. R. (Hospital No. 7893, O.P.D. No. 66695) (Fig.1), boy aged eighteen. The patient's mother had numerous miscarriages; an uncle had catalepsy. The past history was essentially negative; no ordinary diseases of childhood were reported. The tonsils were removed twice at the ages of eight and nine. There were no complaints except underdevelopment physically. The examination showed the boy to be slender, underdeveloped, with muscular and sexual appearance of about ten years; he had high-pitched voice, no secondary sex characters, no hair on face, axillae or pubes, small penis and testes, and only a very small amount of prostatic tissue, barely palpable. The patient passed all the Binet-Simon tests, even adult, without missing one; there was no mental defect. The laboratory findings were: Blood pressure, 118/60; urine, negative; blood picture, normal; blood Wassermann, negative; spinal fluid, negative; Von Pirquet, negative; blood

sugar curve, .03, .224, .127, .076; urine sugar curve, negative, negative, positive, negative; radiograms showed extensive peribronchial thickening and sella turcica somewhat small. The patient is under observation and is receiving increasing doses of anterior lobe pituitary.

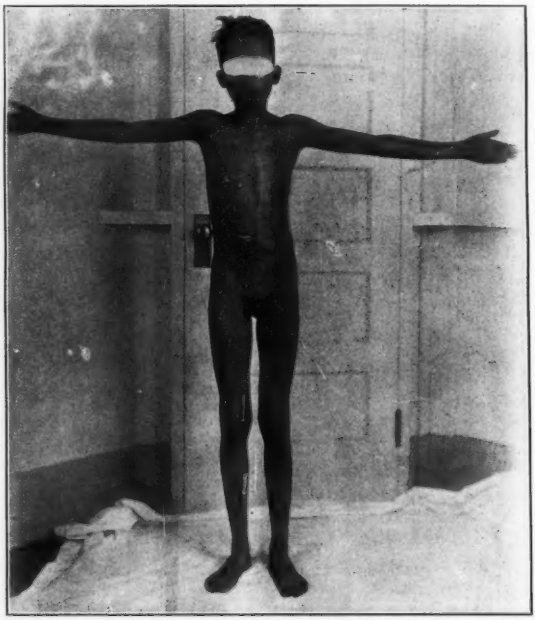

Fig. 1. Case I. Patient eighteen years old; skeletal undergrowth with infantile genitalia; complete absence of secondary sex characters; sella small. Typical case of Lorain infantilism.

CASE II

Miss M. McD. (Hospital No. 9257, O.P.D. No. 66375.) (Fig. 2), is 44 years old. She was born and has lived all her life in San Francisco. She had measles, scarlet fever, whooping cough in childhood, pneumonia three times recently; acute arthritis recently. *She has never menstruated;* has always been severely constipated; always been pale, always cold.

Examination shows a small, slender, short woman with peculiar thick, deep, masculine voice; height, 145 cm.; upper measurement, 67 cm.; lower measurement, 78 cm.; skin, dry, thin and wrinkled; hair, plentiful on scalp, but very scanty eyebrows, axillary and pubic hair; saddle nose; expressionless eyes with heavy eye-lids; many wrinkles around eyes and mouth and forehead; facial appearances monkey-like;

thyroid not palpable; breasts practically undeveloped; infantile external genitalia; no uterus palpable rectally; cordlike mass spanning pelvis suggesting rudimentary uterus; small round object size of bean in right broad ligament, probably ovary. The blood pressure, is 90/60; urine, negative; blood count indicates marked anemia; Wassermann in blood is negative; spinal fluid, negative; radiograms show a normal sella turcica and epiphyses of hands and feet, joined; sugar curve, normal; basal metabolism, 6% below normal; mental examination, age 9.

Fig. 2. Case II. Patient forty-four years old; never menstruated; infantile genitalia; cretinoid face with saddle nose; mental age nine years; blood pressure 90/60. Case of Lorain infantilism and infantile myxedema.

This patient shows pluriglandular deficiency involving pituitary thyroid, ovaries and suprarenals. The face is cretinoid but skeletal undergrowth without adiposity and aplasia of the genitalia resembles those of Lorain infantilism.

CASE III. PREADOLESCENT FRÖHLICH'S HYPOPITUITARISM ASSOCIATED WITH FEEBLEMINDEDNESS AND ABSENCE OF THE PROSTATE

R. H., aged 10 years (Fig. 3 B). He was one of twins born at full term; he first talked at the age of two and a half years, first walked at three; always was fat and heavy; never played with other children; was good-natured; mentally apathetic, eyes always crossed; could not read, only spoke phrases, no sentences; neither constructive nor

Fig. 3. Cases III and IV. Twins aged ten; identical examples of Fröhlich's dystrophy adiposo-genitalis. Mental age three years; note girdle obesity and infantile genitalia; prostate absent.

destructive; had ravenous appetite; was sleepy. He had measles, pertussis, pneumonia three times, circumcision, tonsillectomy and adenoidectomy. He had large quadrangular skull, coarse dry hair; female contour with broad pelvis, enlarged mammae, marked mons veneris; external genitals of female type with penis in position of enlarged clitoris, no hypospadias, external genitals infantile; no prostate palpable rectally; large feet and pudgy hands with marked muscular hypotonicity; *tache cerebrale*, dermatographia.

The mental age was from three to four years, or six years' retardation. The laboratory findings were: Blood pressure, 118/62; urine, negative; blood picture, negative; Wassermann, negative; Von Pirquet, negative; blood sugar curve, fasting 0.103 per cent, one half hour later

0.129 per cent, one and one-half hours later 0.107 per cent, two and one-half hours later 0.088 per cent; renal sugar curve, negative; eye fundi normal; radioscopy showed normal skull and hands.

This boy and his twin brother (Case 4) are being kept under observation and one is receiving increasing doses of whole gland pituitary extract, while the other is not receiving any treatment, serving as a human control. Their cases will be published some time later in more detail, since in addition to the absence of the prostate, these twins are of extraordinary interest from the fact that they show identical endocrinopathies, suggesting that the pathological factor must have operated in the earliest cell division.

CASE IV. PREADOLESCENT FRÖHLICH'S HYPOPITUITARISM ASSOCIATED WITH FEEBLEMINDEDNESS AND ABSENCE OF THE PROSTATE

W. H., (Hospital No. 7892, O.P.D. No. 67081) (Fig. 3-A), boy, twin, aged 10. The history, physical examination, mental examination and laboratory tests were in every respect precisely similar to the findings of the twin brother (Case III) recorded above, except that the brother was fatter, weighing seven pounds more, and was one inch taller. The figures for the blood sugar curve was 0.116, 0.149, 0.139, 0.106.

CASE V

Private patient, Mrs. L. J. T., aged 28. The family history was negative. She had measles, whooping cough, chicken-pox, diphtheria, scarlet fever in childhood; mumps, at 23, without complications; pleurisy and influenza; menstruation began aged 11, was always very irregular, skipped three and four months at a time until marriage, at 24, then was fairly regular for a year; she then became pregnant; since the baby's birth menstruation has again been irregular and scanty, but the patient claims that two tablets of lutein will bring on a period and produce profuse flow; she is very gloomy and depressed approximately coincidentally with the periods, but at all other times is very jolly. At eleven, just prior to puberty, she weighed 120 pounds, was very stout; at 14 was quite thin, weighing 100 pounds; between 14 and 24, the year of her marriage, she gained steadily, and recently, quite rapidly, to 201 pounds, a gain of 50 pounds in two years. The fat accumulated almost entirely around the hips. The patient is now always sleepy, easily fatigued, has little energy, is usually cold, bruises readily, has no polyuria or polydipsia. Sexual desire and gratification are markedly diminished.

Examination shows height, 5 feet 5½ inches; weight, 201 pounds; fat is principally on hips; skin and hair normal; urine negative; blood pressure 110/80; sella turcica, by radioscopy, small.

Diagnosis: Post-adolescent hypopituitarism.

CASE VI

Private patient, Miss M. C., aged 18 years (Fig. 4). Family history was negative. She had measles, mumps, whooping-cough, chicken-pox in childhood; at 2½ years she suddenly became lame in the right leg, the right hip was operated upon in 1915; tonsils and adenoids were removed in 1919; she was always thin until July, 1919. In May, 1919, she weighed 128 pounds; from July, 1919, to October, 1920, she

increased 60 pounds, although she eats sparingly. Menstruation began at 14, was never regular, sometimes came three weeks interval, sometimes five weeks; during 1919 she missed five periods in succession; since July, 1920, she has menstruated but once. She was given thyroid gland by a physician during the early part of 1920, following which, she became very nervous and short of breath, had palpitations, tremor and rapid heart.

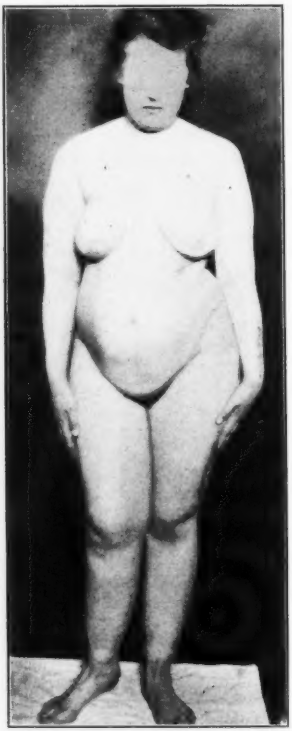

Fig. 4. Case VI. Patient eighteen years old; obesity with amenorrhoea. Fröhlich's syndrome.

Examination: Height is 5 feet, 4½ inches; weighs 185 pounds; she is very obese, especially in breasts, hips and abdomen; hair is scanty in axilla and pubic regions; skin is fairly normal; she has rapid, fine tremor; pulse, 120; slight symmetrical enlargement of thyroid with bruit; marked hypotonicity of joints; blood pressure, 145/75; urine normal; basal metabolism 11.4 per cent above normal;

sella turcica as disclosed by radioscopy, possibly slightly small but maybe within normal limits.

Diagnosis: Fröhlich's syndrome, with therapeutic hyperthyroidism.

CASE VII

Mrs. L. K., O.P.D. No. 72211, aged 37 (Fig. 5). Her family history and past history are unimportant. She was married at 16, and has one son, aged 18 years. She has been pregnant but once. Menstruation began at 11, was always regular, every 28 days, flowing rather profusely eight or nine days, until five years ago, when menstruation ceased, at 32. At the age of 23 she weighed 115 pounds; at

Fig. 5. Case VII. Patient aged thirty-seven years; menstruation ceased at thirty-two; sella small; marked obesity. Post-adolescent hypo-pituitarism.

32, when menstruation ceased, 170 pounds; her present weight is 190. She bruises easily, and is cold most of the time.

Examination: She was a short, very fat woman, 5 feet 1 inch in height, weight, 190 pounds; skin of face and arms rough and coarse; big breasts and abdomen; very fat thighs; hair normal; narrow palpebral aperture; uterus and ovaries small; blood pressure, systolic 110; basal metabolism, 5.5 per cent below normal; calvarium by radioscopy, thick; sella small.

Diagnosis: Post-adolescent hypopituitarism with slight hypothyroidism.

CASE VIII

Mrs. R. H., O.P.D. No. 68337, 34 years old, negress (Fig. 6). Her family history is negative. She had measles, mumps and whooping-cough in childhood; pneumonia at 14; typhoid fever at 17, from which she took nine months to recuperate. Menstruation began at 14, was regular up to the age of 18; then missed ten months following typhoid

Fig. 6. Case VIII. Negress aged thirty-four; obesity and amenorrhoea following typhoid fever; small sella; note girdle obesity. Post-adolescent hypopituitarism.

fever; then regular again until 29; then missed for one year without apparent reason, except that she grew very stout at that time, gaining from 150 to 210 pounds, the most she ever weighed. She began to menstruate again at 30, and promptly lost 25 pounds, weighing 185; then menstruation was regular until two years ago at 32; there has been no menstruation since that time but the breasts get full and tender each month and she becomes very nervous and emotional with crying spells. Sexual desire and gratification are unimpaired. She becomes easily fatigued and sleepy.

Examination shows "pituitary" obesity; urine normal; flat skull, small sella turcica (by radioscopy.)

Diagnosis: Fröhlich's syndrome, probably following typhoid fever.

CASE IX

Mr. A. C. R., private patient, 47 years of age (Fig. 7). The father's age was 53, and the mother's 43 when the patient was born. One brother shaves very rarely, the other does not shave at all; both brothers are married and have children. The patient has two sisters; one is married and has children. He had measles and mumps as a child; influenza in 1890; typhoid at 37. He has been married 15 years; the wife is well; there have been no pregnancies. In the past four years he has had four peculiar fainting spells usually associated with emotional excitement; there have been no convulsions; he does not bite his tongue or have incontinence of urine or feces.

Examination shows weight, 185 pounds; high-pitched voice; cheeks, chin and upper lip entirely devoid of hair (he has never shaved); body

Fig. 7. Case IX. Man aged forty-seven; note girdle obesity; feminine configuration; marked development of breasts; feminine type of pubic hair; infantile genitalia; has never shaved. Fröhlich's syndrome.

of characteristic feminine contour with abnormally developed breasts; prominent mons veneris and typically feminine hips and thighs; the pubic hair is somewhat scanty and of feminine distribution; axillary hair is very scanty. The external genitalia are infantile, resembling those of a boy of eight; the testicles are decidedly small. He has never obtained satisfaction from sexual intercourse. The skin is dry and never perspires; the thyroid is slightly enlarged. He says he had a goitre 12 years ago, which was painted twice a day with iodine and disappeared. The blood pressure is 110/75; urine, normal; blood count, normal; sella turcica, by radioscopy, small; basal metabolism 26.4 per cent below normal.

Diagnosis: Fröhlich's syndrome, originating prior to adolescence.

CASE X

L. Z., O.P.D. No. 73098, aged 51 (Fig. 8). The father died at 80. The patient's height is 6 feet and the weight 250 pounds. No other member of the family, including the mother and four brothers, have any similar disturbances. The past history is unimportant. The patient noticed that he was different from other boys because they poked fun at him on account of his large breasts and small genitals. He has never shaved. The voice is high-pitched. He has never had any sexual desire or erections or intercourse. He was tall for his age and as a boy was fat. He was 6 feet tall at 16 years. He was always very strong

Fig. 8. Case X. Man fifty-one years old; skeletal overgrowth with infantile genitalia; Neurath-Cushing type of dyspituitarism; never shaved; very small prostate.

and powerful; being sensitive about not being like other men he always sought very strenuous physical labor, such as that of a sailor; he did deep water diving. His case in 1914 was diagnosed by Dr. Barker at Johns Hopkins as "acromegaly and infantilism." At that time he had excruciating headaches with explosive, projectile vomiting. Dr. Cushing and Dr. Horrax of Harvard saw him in 1917, and because of vomiting and headaches decompression was done, apparently a subtemporal—which absolutely relieved the headaches and vomiting almost immediately; he has had none since. Drs. Rigdon and Stanley performed

transplantation of human testicle into the scrotum in December, 1919. He was demonstrated last year at the California State medical meeting in Santa Barbara. He had several erections within 24 hours following operation, the first he ever had in his life; the transplant did not slough but gradually atrophied; three months following operation he had intercourse successfully twice. There had been no hair whatever on his face prior to the transplantation, but it began to grow about a month later and can be seen in present pictures although he has never shaved—he wants to grow a beard. There has been no hair between the umbilicus and symphysis until recently; there is some present now and also more pubic hair; although he formerly never perspired, the skin has become smooth and moist. While he was with Dr. Barker in 1915, the prostate was searched for and only a very small organ found; for present appearances see figure.

Diagnosis: Neurath-Cushing type—skeletal overgrowth with adiposity and genital infantilism.

The above cases illustrate the principal types of hypopituitarism as they occur both prior to and after adolescence in the male and the female. No partial pictures have been included, such as diabetes insipidus, pituitary psychoses, pituitary epilepsy, pituitary headaches, and pituitary cachexia.

As regards the latter, several cases have been reported in recent years, especially by German clinicians, of extreme emaciation with eventual death, autopsy showing no cause whatever for the condition except extreme atrophy and almost entire absence of the anterior lobe of the pituitary. This would seem to suggest that the anterior lobe can exercise a considerable influence on metabolism, and makes one pause before ascribing the metabolic disturbances to the posterior lobe alone. These findings are, however, very difficult to reconcile with the therapeutic result achieved by Roblee, previously alluded to, in which feeding of the anterior lobe alone, to a subject having Fröhlich's syndrome resulted in fifty pounds loss of weight. This matter is briefly mentioned here merely to illustrate the complexity and uncertainty of our knowledge at the present time regarding the functions of the pituitary lobes.

THE ETIOLOGY OF HYPOPITUITARISM

The several varieties above described and illustrated are all the result of pituitary disease. The cause of this pituitary disease is by no means always the same. In the first place, an hereditary factor probably bears some influence in many instances. It is not unusual to discover similar ductless gland disturbances in other members of the family, either in brothers or sisters or in father and mother, uncles and aunts, etc. In such cases we are probably dealing with some defect in the development of the gland. Other instances of hypopituitarism would seem to originate following an acute infectious disease, the infection, as it

were depressing functional activities. A tumor of the pituitary may produce any of the pictures described above. Injuries to the gland either from a foreign body such as a bullet or secondary to fracture of the base of the skull have been reported as responsible for various examples of hypopituitarism and finally lowered pituitary function may be a secondary result of diseases originating in other ductless glands. Injury to the testicles, for example, with consequent atrophy may indirectly result in hypopituitarism as well. An actual infectious disease of the pituitary itself, as syphilis or tuberculosis, may give rise to manifestations of hypopituitarism. Instances have been reported in which anti-luetic treatment of a pituitary gumma has resulted in disappearance or at least marked amelioration of the hormonic disturbance. Probably there are still other causes of hypopituitarism not mentioned above but they may be regarded as somewhat speculative whereas those above recorded have received abundant confirmation.

THE PROGNOSIS OF HYPOPITUITARISM

Obviously this will depend on the nature of the pituitary lesion. If the lesion be a tumor, the treatment becomes a surgical problem; if syphilitic, a matter of anti-luetic treatment; if a congenital lack or if post-infectious, then the treatment will be that of organotherapy. And until this therapy has advanced considerably beyond its present status the prognosis will be exceedingly uncertain. It is equally apparent that the outlook will depend upon the degree to which the hypopituitarism has advanced, which includes both the number of years after onset and the actual age of the patient when seen. Some of the signs and symptoms will be more susceptible to treatment than others.

In a general way the chances of restoring normal function will be brighter (in a case of preadolescent hypopituitarism) if the condition is recognized and treatment undertaken prior to puberty, since the likelihood of developing normal external and internal genitalia is decidedly less favorable after adolescence has once passed by. Early diagnosis and long continued treatment give the best hopes for recovery.

THE TREATMENT OF HYPOPITUITARISM

Let us dispose first of those cases that are due to tumor. Once the diagnosis of neoplasm has been made such patients should be

promptly reported to the surgeon for removal of the growth if possible and otherwise for decompression. Whether after removal or decompression pituitary therapy should be instituted to substitute for whatever glandular lack there may be is a question to decide in each individual case. It does not seem unreasonable to suggest, however, that such additional treatment might occasionally be of value.

Possibly it would be wise in most cases of hypopituitarism to search for and remove foci of infection such as infected tonsils and apical tooth abcesses, etc. This is mentioned because it would seem as reasonable to do so in hypopituitarism as it has become customary to do so in hyperthyroidism. The assumption for such a procedure is naturally based upon the idea that the absorption of toxic products from infectious foci may at times either excite or depress hormonic activity. Proper conservatism is, however, advisable.

We may now properly consider the subject of specific pituitary organotherapy. At the outset it seems to me only fair to state quite frankly that we are still floating about somewhat hesitatingly in what is largely an uncharted sea. Organotherapy is our latest fad in medicine. At times pituitary therapy gives brilliant and most gratifying results. Often it is extremely uncertain if not positively absurd. Judicious conservatism and scrupulous honesty are indeed most urgently needed but often lamentably lacking. The superficial enthusiasm now so rampant will not aid us in finding our landmarks and in charting our way,—rather do they serve to bring the entire subject into disrepute. In the first place, we have no adequate ideas of dosage, none comparable with those that guide us in administering thyroid extract. For instance, shall we prescribe one grain of anterior lobe, let us say, three times a day, ten grains three times a day, as Roblee did, or one hundred grains three times a day, as has Cushing. The careful clinician has many signs and symptoms at his disposal which can guide him in estimating the dosage of thyroid extract. No such criteria have as yet been discovered in the case of the pituitary. We may pour in tablets or capsules in large doses without any particular notion of whether we are benefiting or harming our patient. This is not invariably the case but it happens with sufficient frequency to make pituitary therapy quite uncertain, at times bewildering and often disap-

pointing. It is only fair to state that Englebach has suggested control of posterior lobe administration by fixing the dosage at that amount at which the patient has intestinal cramps and diarrhoea about fifteen minutes after injection. This may prove to be a helpful index but as yet it is the only method of control suggested. How meagre this is when compared to the many toxic signs of overdosage from thyroid—such as tachycardia, tremor, sweating, diarrhoea, loss of weight, nervousness, bruit, eye signs and increased basal metabolism.

In particular it should be noted that the literature is rather unsatisfactory, often quite superficial and fragmentary. One may find numerous statements to the effect that "under pituitary therapy improvement was noted," but rarely any painstaking details regarding the exact dosage administered, the duration of the treatment, the particular commercial brand used nor the form in which it was given, whether tablet, powder or liquid, and whether by mouth or by hypodermic injection. The greatest need at the present time is the recording in a straightforward, scientific manner of many cases treated over a long period of time. The haphazard use of pluriglandular formulas although plausibly recommended and occasionally beneficial will not yield in the long run that type of accurate clinical information that is so urgently needed in ductless gland therapy. I have already indicated that our knowledge of the specific functions of the anterior and posterior lobes and pars intermedia of the gland is neither complete nor irrefutable. We can not be sure therefore whether the products of the posterior lobe or the anterior lobe are indicated in an individual case. The solution of lumping them together so as not to miss the one that is needed will not help us in the future to be more accurate and if these products are powerful we may actually be mixing a little harm with a little good. Surely then if administration of bilobar products involves a degree of uncertainty in interpreting results, how much more confusing and complex do we make our problem by the addition of two or three gland extracts simultaneously, even though we know that the corresponding glands may be partly at fault. Under these circumstances it would seem more prudent to prescribe one gland and preferably one lobe at a time and for a long enough time and in gradually increasing dosage so that one may arrive at a definite opinion as to what has been accomplished in a given

case. If the results have been satisfactory well and good; if not, then it is time to begin with another extract and observe its effects. Only in this way it seems to me can we follow in reasonably precise manner what we are attempting to do. Even then we are confronted with the perplexities that surround all medical administration. We should be frank about the brand of preparation used, not with the idea of advertising it if successful or condemning it if disappointed, but because different firms manufacture by different methods. Moreover, the dosage of different firms is not always equivalent,—for example, one grain of Burroughs and Wellcomb's organic extracts does not correspond with one grain of Armour's or of Parke-Davis. Whether the uncertain results of pituitary therapy are due to methods of manufacture or whether the hormones present in the finished products are at times destroyed or altered in the stomach and not properly absorbed is not yet clear, but whatever the explanation, on the whole the results of pituitary administration are by no means as satisfactory as the results from administration of thyroid extract.

It is not my intention to leave the impression that pituitary therapy is always disappointing; rather would I repeat that it is as yet somewhat uncertain. Brilliant results of the most gratifying character occasionally reward one, but why success attends its administration in one case and comparative failure in another is difficult to explain. One should not place too much confidence in subjective improvement as reported by the patient. On the other hand, it would not be fair to disregard this feature of our therapy entirely. Patients frequently report more energy, more strength, less sleepiness, and other encouraging symptoms of improvement, but we should be more influenced by objective phenomena such as loss or gain of weight, redistribution of fat, changes in mensuration, growth of body hair, return of menstruation, or sexual potency, pregnancy, changes in temperature and blood pressure and improvement in mental age as indicated by Binet-Simon tests—it being understood that the latter are computed by the same observer in any given case, if possible.

In conclusion let me report very briefly a few personal experiences of cases observed sufficiently long perhaps to warrant mention at this time.

The boy of eighteen with Lorain infantilism (Case 1) has received pituitary anterior lobe extract. Treatment was begun September 3, 1920, and has continued until March 4, 1921, or six months. At first one grain of B. & W. anterior lobe pituitary extract twice a day was given. This was gradually increased until he was taking twelve grains daily. After four months a change was made to Armour's anterior lobe pituitary of which he took six grains daily equivalent to about thirty grains a day of the B. & W. preparation. During this six months there was absolutely no change in the patient's appearance, particularly no development of the genitalia or secondary sex characters. There was no increased growth of hair nor did his voice begin to change to a lower pitch. He grew one inch and a half during this six months and gained seven and a half pounds. This was the only result noticeable and whether this gain in weight and growth of one and a half inches is justly attributable to the pituitary he received or would have occurred in the normal course of events is open to question, although it may be noted that he had remained for two years prior to the beginning of treatment at exactly the same weight. During the last month of observation he received four injections in addition of antuitrin, a liquid extract of the anterior lobe recently introduced by Parke-Davis. If Lorain infantilism is a pure anterior lobe deficiency as suggested by Engelbach, then pure anterior lobe feeding is the therapy indicated. Possibly the above dosage has been too small, possibly if circumstances were different permitting daily injections of antuitrin better results might be achieved.

The twins whose pictures were shown as examples of preadolescent dystrophy adiposo-genitalis, on the basis of bilobar deficiency were given increasing doses of whole gland pituitary extract. They have been under observation for almost eight months, taking the medicine steadily and receiving as high as thirty grains a day of B. & W. pituitary substance. Possibly there has been a slight change in redistribution of fat, their abdomens appearing to be less prominent, but in any case the change has not been striking in this regard nor has there been any development of the genitalia. The twins were ten years of age with a mental age of three years when treatment was begun and at the end of five months their mental age had been increased one year—the tests being executed by the same person. However, here again it is only fair to state that during this period

they had been in a special private school for defective children under close personal supervision and instruction by a trained teacher. Whether this change in environment and special instruction has been responsible for their mental improvement or whether the pituitary extract has been a factor is difficult to judge. Unfortunately the simple experiment did not occur to me until it was suggested just recently of giving pituitary to one of the twins and none to the other, using the latter as a control. This has just been started and it is too recent a change to warrant any positive statement at this time, but should prove an interesting therapeutic experiment.

Case V, the married woman, aged 28, who gained 50 pounds in two years following pregnancy and whose obesity was of the girdle type, whose menstruation became irregular and who was very sleepy and easily fatigued, began treatment a month ago. Her dose of whole gland Armour's pituitary has been increased to ten grains daily and during this time she has also received fourteen injections of posterior lobe extract B. & W. Subjectively there has been striking improvement. She voluntarily insists that she is far more active and energetic—more cheerful, and no longer sleepy, and has also noticed marked return of sexual desire and gratification. She has lost eight pounds in weight and the chest circumference and breast circumference have been reduced one inch and the hip circumference one and one-half inches. This is an encouraging beginning.

Case VI, single girl aged 18, who gained 60 pounds in the previous year and who has menstruated only once in the past ten months, began treatment seven months ago. She received during the first six months injections of whole gland pituitary extract B. & W., six injections of posterior lobe Parke-Davis and eighteen injections of posterior lobe B. & W., and gradually increased amounts of whole gland pituitary—Armour's, up to fifteen grains daily, which dose she took for eight weeks and which is equivalent to about 75 grains a day of the B. & W. fresh gland. During this time she lost 15 pounds, her bust circumference decreased two inches, waist measure two and a half inches, and hips one inch. Subjectively she felt very marked improvement and her family enthusiastically remark upon the change in her disposition, she being brighter and more cheerful and far more active. However,

no effect was had upon amenorrhea except that one menstrual period occurred after four months' treatment, and lasted four days, which was the longest she ever menstruated. Recently she has been placed on pure anterior lobe therapy, and is now receiving 15 grains a day of Armour's anterior lobe and three injections weekly of Parke-Davis antuitrin. It is too early to report on the results of this change of therapy. The change was made because there was no further loss of weight or return of menstruation other than reported above. One might reasonably claim some improvement in this patient and she herself is very much pleased, but the results are far from brilliant as yet.

(Later note.) The anterior lobe medication was increased steadily, and finally for an entire month she received daily injections of antuitrin and 100 grains daily of dried anterior lobe extract (Armour). Absolutely no effect was noted. Menstruation has now remained absent for a year and a half and no further loss of weight occurred.

Case VII, a married woman, aged 37 years, who suffered from complete amenorrhoea for the previous five years was first given thyroid extract. This was administered for three months with no return of menstruation. Anterior lobe (Armour), 15 grains daily, was then begun and the first period in over five years appeared one month later. Thinking she was cured she remained away for three months and discontinued the medicine. She skipped three periods and regained the 20 pounds she had lost. Then she returned for further treatment. For six months past she has taken anterior lobe (Armour) regularly, gradually reducing from 15 grains to 6 grains daily, and has menstruated regularly and copiously. She has lost 25 pounds in weight and 6 inches around her hips. Treatment in her case has been specific and most satisfactory.

Case IX was that of a man aged 47, with typical Fröhlich's syndrome originating prior to adolescence, who had never shaved, who had infantile genitalia and typical feminine contour. He was under treatment for one year and has received varying doses of B. & W., anterior lobe pituitary up to 30 grains daily. His weight varied, but on the whole diminished hardly any, but there was striking redistribution of his obesity. He formerly wore a number 16 collar, now wears a number 14; his clothes

had to be altered several times, particularly his trousers. He lost two inches in circumference at the level of his breasts, three inches above his breasts, four inches around his hips. There was no change in the appearance of his external genitalia, but a very slight growth of hair appeared on his face and in the public region. A great change occurred in the condition of his skin, which was formerly smooth, inelastic, waxy and cold. He now perspires easily and his skin has more resiliency and is thinner. According to the patient and his wife, there has been an extraordinary change in his character. He has far more energy, is no longer sensitive and retiring, but thoroughly enjoys the company of men, has become more sociable. He has more self-confidence, is cheerful; he and his wife have repeatedly told me that many of his friends comment on the striking change in his manner and appearance.

In conclusion we may say that pituitary therapy is at times brilliantly successful, often worth while and encouraging if persisted in long enough, but sometimes rather disappointing. The great hope for the future lies in the identification and isolation of the actual pituitary hormone or hormones and their manufacture synthetically. This is all the more to be desired because if huge doses are found to be necessary to achieve worth while results, we must be aware of the fact that the supply of animal pituitary is, after all, limited and the expense to some patients almost prohibitive. "In this connection it is interesting to note that approximately five pounds of fresh pituitary glands are obtainable from one thousand head of cattle, which quantity when desiccated, is reduced to one pound in weight." In the meantime until these important discoveries materialize, grants of funds that would permit large doses for many months and even years to patients who could be carefully watched might help to advance our results in this branch of therapeutics.

EARLY OBSERVATIONS PERTAINING TO THE HYPOPHYSIS.*

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"If no use be made of the labors of past ages the world must always remain in the infancy of knowledge." This quotation from Dr. Samuel Johnson applies well to the study of medicine in general and to the subject under discussion in particular. The early literature on the hypophysis contains much that is speculative, but many important facts concerning the symptomatology and gross pathology were discovered and recorded, and then, unfortunately, passed into oblivion.

Owing to the difficulty encountered in collecting and collating these data and separating the important facts from the trivial and useless, one can appreciate the significance of the following statement from Lord Bacon, as paraphrased by Sir Thomas Watson. "The lecturer must not be the ant collecting all things indiscriminately from all quarters, as provender for his discourses, nor the spider, seeking no material abroad, but spinning his web of speculative doctrine from within, but rather the bee, extracting crude honey from various flowers, storing it up in the recesses of his brain and submitting it to the operation of his internal faculties, until it be matured and ready for use."

Possibly the earliest record of a function ascribed to the pituitary appeared in the writings of Galen, who attributed to the gland the power of separating mucus from the brain for secretion.

After Galen, in the second century, no contributions were made to the literature until the year 1543, when Vesalius in support of Galen's view called it the "gland pituitam excipiens" and thought it secreted the mucous discharge of the nose. This idea prevailed until 1662 when Schneider disputed the old theory, stating that the nasal secretion did not originate in the pituitary. Ten years later Lower in a dissertation on the origin of catarrh supported Schneider's view.

* Read before the Association for the Study of Internal Secretions, Boston, June 6th, 1921.

At about this time anatomical studies and case reports with autopsy findings began to appear in the literature. Willis as early as 1684 described anatomical changes of the gland; and Bonetus (1700) observed a tumor of the hypophysis. Rayer in his his article, published in 1823, refers to a number of anatomists, who had observed alterations in the pituitary gland. He quotes Wepfer (1734), who described the normal gland and also noted a case in which the gland was twice the normal size. Petit (1718), generalizing a small number of anatomical observations, believed that the gland *is squirrheuse* in most individuals affected with hydrocephalus.

Morgagni (1766) found that under certain circumstances the glands had a rich yellow color; others were impregnated with considerable mucous material, and again others showed atrophy.

Vicq-d'Azyr (1799) mentioned concretions which he observed in the gland substance. Bichat in his "anatomie descriptive" also encountered them and found the gland hard and almost scirrhus or in a state of suppuration. Chaussier (1812) found in an infant a gland larger than that in normal adults.

The report of Rayer's case observed in 1814-15 is interesting, as he describes with great detail a narcoleptic state now recognized as a symptom of advanced hypopituitarism. The patient, a man 47 years old, was naturally gay and industrious, but recently had become lazy and extremely careless. His ideas were normal and his responses sensible, often thoughtful but slow. The memory was impaired and he complained of a feeling of heaviness in the front of the head, which caused him to rub the forehead and eyes mechanically, as one does ordinarily when awaking. The vision was impaired. He had an insurmountable repugnance for exertion, as getting out of bed. On the morning visit he would promise to rise and dress, but after frequent requests from the nurse during the day, at five o'clock he was usually found still in bed. If forced to arise he would go to sleep in an arm-chair. His attitude was one of extreme weakness, depression and stupor. In the evening he dismissed the nurse and went to bed with most of his clothes on, in order, as he said, to avoid the trouble of putting them on the next day. Finally he was unable to get up and became completely blind, more depressed and stuporous, incoherent, and eventually pro-

foundly comatosed, when blisters to the back of the neck, mustard poultices to the sole of the feet, julep tonic and decoction of quinine failed to revive him. The autopsy showed very yellow and resistant subcutaneous and omental fat, although not excessive in amount. The hypophysis was much larger than normal, measuring a thumb and a half in diameter, and the tissue was dense and amalgamated with a soft pulpy material. The optic nerve was compressed and flattened at the chiasm.

The above case presents a striking similarity to one observed by Ward in 1823. His patient was a man 38 years old, who suffered from frontal headache, stupor and blindness. He had the same tendency to fall asleep when sitting in a chair, and the headache was severe. Leaches, blood-letting and calomel were resorted to for treatment, but the patient died. The pituitary gland was replaced by a tumor which compressed the optic and olfactory nerves (The London Medical Repository, September, 1823, vol. 20, page 217). Based on the records of published cases and his personal observations, Rayer (1823) summed up the knowledge pertaining to the hypophysis at that time in the following deductions:

1. Since the uses of the pituitary gland are not understood, its diseases cannot be determined during life by functional disorders.
2. The pituitary gland is not only altered in structure, but also augmented in size. It compresses more or less the neighboring parts and particularly the optic nerves.
3. This compression produces phenomena which can make one suspect the seat of the disease, such as pain or heaviness at the anterior part of the head, apathy, impairment of memory, weakness, drowsiness, and blindness, more or less complete, most often in both eyes.
4. The diseases of the pituitary gland, like those of the parts of the brain situated in the median line, do not cause convulsions or paralysis of one side of the body. The cause, which has produced the development formed by the pituitary, and this tumor itself finally bring about inflammation of the neighboring parts; also symptoms of cerebral phlegmasia at the end of the disease are added to those of compression.

5. If one cannot hope to be able to distinguish, during the life of the individual, the tumors formed at the expense of the gland and the stem from those developed at the optic chiasm, at least the same difficulties will not present themselves when it is a matter of judging of the diseases of the appendix of the brain compared with those of one of its hemispheres.
6. The diagnosis of diseases of the gland and of the pituitary "stem" is rendered very obscure by the simultaneous existence of one or several other lesions of the brain.

The association of epileptiform seizures with pituitary diseases was probably first mentioned by Raymond Vieussens, 1705. This occurred in the case of "Le cardinal de Bonsy," who died at the age of seventy-two from a tumor of the pituitary gland, the size of a hen's egg. For eleven years previous to his death he was subject to convulsive movements, which especially involved the muscles of the eyes, the lips and the tongue; according to the description they were epileptiform in character. In addition he developed blindness in the left eye, impairment of intellect, especially memory, and died from an apoplectiform attack.

Among other early writers, who mentioned epilepsy in connection with lesions of the pituitary gland, are Greding (1781), who observed anatomical changes in the gland; Wenzel (1810), who observed a tumor and in another case (1811) a reddened and inflamed infundibulum. The latter emphasized the fact that the pituitary possesses an important function and suggested the relation of epilepsy to disturbance of this function.

Amenorrhea as a symptom of pituitary disease was first mentioned by deHaen in 1761. This occurred in a girl 20 years old. She did not menstruate for three months, after which she developed blindness and incessant vomiting, which lasted fourteen days, when the symptoms were relieved by the judicious employment of purgatives. Later amenorrhea, vomiting and blindness reappeared, but as purgatives did not relieve her this time, the actual cautery was applied to the left side of the head, which produced an extensive suppurative wound; the patient died in five days from symptoms of meningitis which the author attributed to the effect of the cautery. The autopsy presented an un-

usual condition. It showed a left-sided meningitis; the infundibulum was enlarged, measuring 8 or 9 lignes (2 cm.) in diameter. It contained pultaceous material and calcareous matter and caused pressure on the chiasm. The blood vessels, especially those distributed to the left hemisphere, contained a large quantity of air. The latter was expressed in italics by Rayer, who cited the case and who further discussed the matter in a footnote. While this observation is purely incidental, it deserves mention because of the possibility of an early recorded case of gas bacillus infection.

Although Morgagni, as early as 1766, has been cited as associating obesity with hypophyseal lesions, the statement could not be verified. However, reference to changes in the color and density of fatty tissue as found at autopsy occur in the early literature of which mention has already been made. Undoubtedly the first authenticated instance of hypophyseal disease with obesity on record is that by Bernard Mohr (1840). He describes a case of fat dystrophy very similar to Frölich's. The patient was a woman 47 years of age, who suffered with disturbance of vision, vertigo, headache, mental deterioration and apoplectiform attack. Besides, an unusual obesity developed with extraordinarily large abdominal dimensions, especially in the transverse diameter. The autopsy showed a very large degenerated pituitary gland and an enormous amount of subcutaneous fat besides an increase of fatty tissue about the heart, liver and mesentery.

Ocular symptoms are given prominence throughout in the early literature, and the most extensive bibliographies are found in the ophthalmological reviews; thus in Graefe-Saemisch Handbuch der Augenheilkunde XI, Band 2, Abt. B, 1915, page 1300-1328, Uhthoff gives three hundred and fifty-nine references to articles which appeared in the literature from 1821 to 1901—the period covered in this article—and six hundred and twenty references to 1910, all dealing with ocular manifestations. Amblyopia and amaurosis are frequently mentioned as the chief symptoms in the earlier cases. Later, with improved methods of diagnosis, various ocular disturbances were recognized, most of which are pressure phenomena, including blindness, exophthalmos, abducens paralysis, neuroretinitis, optic atrophy, diplopia, hemianopsia, etc. Blindness the result of tumor of the hypophysis is emphasized by men like Hedlund (1833), Harvey

(1855), and Leber (1866). "The Ophthalmological Society of the United Kingdom" held a very interesting meeting in 1887 (Brit. M. J., Lond., 1887, Vol. 1, p. 1334), when a case of optic atrophy in one eye and temporary hemianopsia in the other was reported, and the entire syndrome of dystrophia adiposogenitalis, unrecognized as such, occupied the attention of J. B. Story, E. Nettleship, Dr. H. Griffith, Dr. J. Anderson and Dr. Coupland, and pituitary lesions in their relation to eye symptoms, obesity, menstrual disturbances and mental manifestations were discussed. Mr. Story's case was that of a young woman who gradually became blind in the right eye and had temporal hemianopsia in the left. She suffered with headache, vomiting and irregular menstruation. Her chief complaint was daily drowsiness about noon. During the period of observation it was found that she grew stouter. However, at the time of the report of the case she was able to follow her occupation, her general health being fair. It developed that similar cases were brought to mind and autopsies on them revealed pituitary tumor.

Beginning with the first cases recorded, headache is mentioned as one of the leading symptoms of pituitary disease. It is usually described as occurring in the anterior part of the head and is often paroxysmal in character.

Apparently little or no attention was paid to the genital syndrome until Fröhlich associated hypogenitalism with pituitary disease. The anomalies of the secondary sex characters were likewise not recognized.

The year 1886 is significant because of one of the most important contributions to the study of hypophyseal disease by Pierre Marie. The results of his observations were the basis of a thesis which was published under the title of "Two Cases of Acromegaly," an unusual non-congenital hypertrophy of the head and lower extremities in Revue de Medicine in 1886 (Paris, 1886, Rev. de med., vi., 297-333). This has been translated into English and published by the New Sydenham Society in 1891, vol. 87. Marie's essay comprised not only his own cases, but had also reference to a number of others which, unrecognized as a special disease, he had succeeded in finding already recorded in medical literature. The earliest case to which he refers was reported by Sancerotte-Noel. The patient was a man 39 years of age and under observation from 1766-1773, when he died, "after

living too well, from the effects of an overdose of purgative." No autopsy was allowed, but the bones were finally dug up by Sancerotte, and a rib, sternum and clavicle were placed in the Dupuytren museum. The author states that the man was obliged to have his hats made for him, having been unable to find any ordinary shape sufficiently large. His bones became double their former size. The lower jaw measured eighteen inches in length from one condyle to the other, and four inches in depth at the incisors. It rested almost on the sternum and gave the patient the appearance of having no neck. He was almost always sleepy (a symptom which we now recognize as one of secondary hypopituitarism), which was attributed to the thickness of the skull, causing compression of the brain.

Other cases of undoubted acromegaly, prior to the appearance of the first memoir by Marie, were reported by Brigidi, Chalk, Verga, Heurot, Friesche and Klebs under different names, such as general osseous hypertrophy, pachydermatous cachexia, gigantism, ophthalmic cachexia, osteitis deformans, leontiasis ossea of Virchow, etc.

Uhthoff (1915) collected forty-four cases of hypophyseal disease reported in the literature prior to 1886, the time Marie described the syndrome of acromegaly. In practically all of these cases tumors of the gland were found. From the clinical description it was not always possible to determine whether they manifested symptoms of hyperfunction or hypofunction of the gland. However, after the recognition of acromegaly as a distinct entity in 1886 to the time when Fröhlich described the syndrome characteristic of hypopituitarism in 1901, pituitary tumors were roughly divided into two groups: (1) those with symptoms of acromegaly; (2) those without symptoms of acromegaly. The latter group included practically all those cases which are now reported under the caption of dystrophia adiposogenitalis.

Kollarits (1904) found fifty-two cases in the literature of hypophyseal disease without acromegaly, forty-two of which appeared prior to Fröhlich's publication in 1901.

In 1890 Souza-Leite, a pupil of Marie's, published a thesis on acromegaly, which he called Marie's Malady, in which he reviewed thirty-eight cases, seven of which had come to autopsy. He states that the most specific lesion found in all of these cases was an increase in the size of the pituitary body, varying from a

pigeon's egg to that of a hen's egg or even an apple; and of those belonging to the skeleton the most curious was the great deformity and alteration of the pituitary fossa or sella turcica.

The two monographs of Marie and Souza-Leite furnished such a complete description in respect to the clinical manifestations, skeletal alterations and pathological findings that little knowledge on these phases of the subject has been added since. The chief problem which they left unsolved was the physiology of the gland.

The first achievement along this line was the discovery by Oliver and Schafer (1895), who found the pituitary to be a gland of internal secretion, exercising the important function of raising blood pressure, when extract of the whole gland is given intravenously. Howell proved that this peculiar property is present only in the posterior lobe, and furthermore observed that it exerted an inhibiting influence on heart action. During this period of intensive study of the subject it was noticed that the gland is affected during pregnancy—the anterior lobe increasing in size. Rogowitsch (1889) showed that the removal of the thyroid produced hypertrophy of the hypophysis. Then Oppenheim (1899) appears assigning to x-rays an important role in diagnosis, confirming the enlargement of the sella turcica.

The recognition of the syndrome described by Fröhlich (1901) marked another epoch in the history of the development of the knowledge of pituitary disease. His case was that of a boy 14 years of age with a history of headache and vomiting and rapid increase in weight, the fat distributed in a characteristic manner, the genitalia underdeveloped and the pubic and axillary hair absent (Wien. klin. Rundschau, 1901, xv, 883-906). A few years later Bartels gave the name dystrophia adiposogenitalis to this syndrome. This period represents the dawn of a new era during which remarkable strides have been made through intensive studies by means of methods of experimental research. The result of these investigations led to a clearer conception of the physiology of the gland, and established a basis for the various clinical syndromes produced by an arrested or perverted function.

SOME OBSERVATIONS ON WATER AND SALT METABOLISM IN DIABETES MELLITUS

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It is a well known fact that in diabetes mellitus the clinical pictures may be dominated by polyuria and polydipsia. It is also well known that in diabetes insipidus the same symptoms are observed and the question arises whether a relation exists between the two diseases.

This question has been often raised and has given rise to a rather extensive literature. That a relation exists is made probable by certain cases that have been described, in which one disease changed into the other [Senator (1), Lewin (2)]. On the other hand, Naunyn (3) denies any relation between diabetes mellitus and insipidus, and Umber (4) states that it has never been proved that in a case of polyuria and glycosuria a real diabetes insipidus existed. Nevertheless, it is remarkable that patients with diabetes insipidus not seldom give a family history of diabetes mellitus.

Trousseau (5) considered this fact important enough that he prefaced his clinical treatise on polydipsia with the words: "Le diabète non sucré peut survenir chez des individus nés de parents qui avaient été polyuriques, glucosuriques ou albuminuriques." Balient (6) described a case of typical diabetes insipidus with hyperglycemia in which a diet free from carbohydrates had a good effect. In some cases of diabetes insipidus in which no glucose is excreted by the kidneys, he advises a determination of the amount of blood-sugar. This is the only way to distinguish between the two diseases.

Teschemacher (7) also believes in a relation between the two diseases and describes some cases in which one form changed into the other. Von Noorden (8), though denying a relation, admits that there have been cases of diabetes mellitus in which, long before glucosuria occurred, marked polyuria with urine of very low specific gravity was seen. He also quotes examples of experimental lesions of the pancreas giving rise to polyuria without glucosuria. Gerhardt (9) and Weber and Grosz (10) be-

lieve that in cases in which both diseases are seen in one family the nervous disposition is hereditary, but that this is no proof that diabetes insipidus and mellitus bear any relation to each other.

If we ask whether a relation between both diseases is "a priori" probable, we must answer that the existence of such a relation may not be considered impossible. Until recently it was generally accepted that the hypophysis played an important part in the pathogenesis of diabetes insipidus. In some cases data given to prove this are not very convincing.

The proofs given by Sekiguchi (11) of the hypophyseal origin of polyuria in cases of carcinoma of the breast are not at all convincing. The same can be said of most publications on the subject [Hoppe-Seyler (12, 13), Newmark (14), Meyenburg and Mason (15), Marañón (16), and others]. Hoppe-Seyler, however, is rather careful in his expressions and admits the existence of a diabetes insipidus without lesions of the hypophysis. A very remarkable case may be mentioned here. Luzzatto (17) reports a case of diabetes insipidus caused by a hemorrhage into the hypophysis. Necropsy disclosed no changes in the brain. Such a case may perhaps prove that in extremely rare instances the hypophysis alone may be the cause of diabetes insipidus. Cushing and Biedl in their monographs suggest that the hypophyseal hormone ascends by the tuber cinereum to act on the proximal mesencephalic centers, and Marañón (18) calls this suggestion very probable. I cannot agree with this. The fact that complete removal of the hypophysis does not cause polyuria affords convincing evidence against this contention. The work of Camus and Roussy (19, 20), of Leschke (21) and of Aschner (23) has proved that lesions of the brain near the tuber cinereum may produce polyuria and diabetes insipidus. Tumors of the hypophysis only give rise to diabetes insipidus when they press on the base of the brain. Anatomically as well as experimentally, the existence of a center for water metabolism near the tuber cinereum has been proved. In the same way the probability of the importance of the hypophysis in the pathogenesis of diabetes mellitus has become smaller and smaller. It has been proved that the so-called hypophyseal diabetes probably has its origin also near the tuber cinereum. The frequent combination of acromegaly with glycosuria does not speak against this.

Loeb (24) had observed as early as 1898 that acromegaly, caused by a tumor of the hypophysis, was only complicated with glucosuria when the tumor had reached a certain size and that when, by some cause or other the tumor became smaller the symptoms of diabetes mellitus disappeared. Loeb rightly concluded that this hypophyseal diabetes was caused by pressure on the third ventricle, a view confirmed by recent investigations.

We have thus a right to believe that if the centre for the water and sugar metabolism near the tuber cinereum are not identical, they are situated close to each other. It is the same with the centre in the fourth ventricle. The piqure of Claude Bernard proves this. Claude Bernard knew perfectly well that this operation could produce polyuria as well as glycosuria. The anatomy of the sugar centre shows how complicated these things are. Dresel and Lewy (25) proved that there are sympathetic cells in the pars posterior of the nucleus dorsalis vagus. When they are stimulated they cause sugar mobilization and hyperglycemia. The pars anterior of the nucleus dorsalis vagus contains parasympathetic cells. When they are stimulated the formation of glycogen is increased. Both centres are influenced by a higher centre in the so-called nucleus periventricularis. As mentioned above, the sugar centre in the fourth ventricle must be in close relation to the water centre. It is possible that another sugar centre is situated in the corpus striatum, but too few facts are known to justify a discussion as to whether this has any relation to the water metabolism.

From these statements it may be concluded that a relation between diabetes mellitus and insipidus is not "a priori" absurd. To attain more certainty it is necessary to study the character of the polyuria in both diseases. In diabetes insipidus some authors believe that the kidneys have lost their power of concentration. Whether this is due to a renal lesion or not is of no importance in the present connection.

Whether the polydipsia or the polyuria is the primary condition will not be discussed either. The fact is that large quantities of urine of very low specific gravity are excreted. Different authors disagree as to the mechanism of this process. Umber (l.c.), Tallquist (26), Erich Meyer (27, 28), Kennaway and Mottram (29), and others state that the concentrating power of the kidney for solids has disappeared.

Gorke (30) believes that this is true only for NaCl, and that the effect of pituitrin is due to an increased concentrating power of the kidney for this substance. Lichtwitz and Stromeyer (31) state that sodium chloride cannot be excreted in normal concentration, but nitrogen can; Forschbach and Weber (32) describe a disturbed function of concentration for some substances only. Other authors, however, are of an opposite opinion. Hecht (33) describes a highly interesting case of diabetes insipidus, which was caused as a Herxheimer's reaction after an injection of salvarsan in syphilis. From this case and from the literature, he concludes that in diabetes insipidus the function of concentration of the kidneys is absolutely normal. Nicolaysen (34), and Barach (35) also describe a sufficient power of concentration by the kidneys.

Socin (36) observed that all NaCl ingested was quickly excreted, giving rise to an increased diuresis. When the patient was allowed to take as much water as he liked, the amount of chlorine in the blood was normal; if the quantity of water was restricted the rise of the amount of chlorine was enormous—even to 1.03 per cent! Goldberg and Herz (37) found that the power of concentration was rather good. They were able by giving NaCl to increase the concentration of the urine threefold. Rosenbloom and Price (38) conclude from their work that there are cases in which the renal concentration power is lost and others with a real polydipsia in which this function is normal. How complicated this question is is shown by a highly interesting article of Bauer and Berta Aschner (39). They describe quite a number of mechanisms of diabetes insipidus. One feels inclined no longer to consider diabetes insipidus as a disease entity, but as a symptom of different diseases.

Veil (40) has described two different forms of diabetes insipidus. The first shows an increased quantity of chlorine in the serum; the second hypochloraemia. Pituitrin has a temporary influence only in cases with hyperchloraemia. In the other cases pituitrin has no influence whatever. It is a well known clinical fact that there exist cases of "pituitrin-feste" diabetes insipidus; this has been once more specially referred to by Bauer and Aschner (l.c.). Some other remarkable experimental facts have been discovered by Veil (41). Piqure of the fourth ventricle gives polyuria, hyperchloruria and hypochloraemia; piqure of

the midbrain is followed by polyuria, hypochloruria and hyperchloraemia.

In relation to these different opinions, it must be borne in mind that such work in patients with diabetes insipidus is not always easy, on account of the virtuosity of such patients in stealing water. We may thus conclude that probably there exist at least two types of diabetes insipidus.

We may now consider what are the characters of polyuria in diabetes mellitus. Not much literature has been published on this subject. Beard (42) and Beard and Rowntree (43) found that in some cases chlorine may be retained in the serum and that these cases may be complicated by edema. Nelson (44) estimated in a number of cases the excretion of nitrogen, chlorine, calcium and magnesium, but though he found some interesting facts they have no relation to our subject. The books on diabetes generally do not mention these matters. Cammidge (45), who considers them briefly, comes to no conclusion. Allen (46) devotes a short chapter to them, but cites no conclusive data. Frerichs (47) states that in diabetes there is hyperchloruria and that this is due to an increased quantity of chlorine taken by mouth. The only remark I found in the literature in which the question is put in a right way is in a study of Leschke (48). He carried out experiments on the concentration-power in diabetes mellitus with polyuria and came to a belief in a similarity between the excretion of water and salts in diabetes mellitus and diabetes insipidus. However, he devotes only a few words to these experiments.

I have been able in three cases of diabetes mellitus with polyuria to study the excretion of water and salt. Of the historia morbi I shall mention only these facts that are of importance as indicating the severity of the cases. The number of cases studied in these experiments is limited to three patients, because it is possible to work only with patients who may be expected not to try to deceive doctor or nurses. If a patient will not be honest the most severe isolation will be useless.

Case I. Teacher, 32 years of age. For three years polyuria, polydipsia, and polyphagia have been noted. Urine is frequently passed. When I saw him for the first time his urine contained 9 per cent glucose, much acetone and diacetic acid. After 10 days, "Mehlfrüchtekur" acetone had disappeared; diuresis (7 liters) with 4.2 per cent glucose persisted. For 4 days the following diet was given: Bread,

80 gm.; milk, ½ liter; veal, 150 gm.; 1 egg, 50 gm. unsalted butter, 500 gm. of spinach or endive. This diet resembles that of Forschbach and Weber. No salt was added to the vegetables. The NaCl content of this diet is about 1-2 gm. daily. The patient did not protest against this tasteless food. It is, if possible, desirable to give this diet for some days since, as has been shown by Borelli and Girardi (49), a NaCl equilibrium is only slowly reached. The fifth day every 2 hours (during the day time) the urine was collected, measured and examined. The estimations of specific gravity, as found in diabetes insipidus literature, has of course little importance in diabetes mellitus since it is too much altered by the presence of glucose.

TABLE 1

Hour	Quantity of Urine (c. c.)	NaCl in %	NaCl in Gm.	Quantity of Water Taken (c. c.)
8–10	600	0.01	0.06	1000
10–12	850	0.009	0.0765	800
12– 2	720	0.013	0.1236	800
2– 4	800	0.017	0.136	600
4– 6	450	0.008	0.036	700
6– 8	670	0.024	0.1608	400
8–10	380	0.01	0.038	1000
10– 8	2750	0.008	0.2200	1760
	7220		0.8509	7060

The most important conclusion that may be drawn from this table is that the patient is reliable. The quantity of water taken and excreted do not show an important difference. Some water is also excreted extrarenally. The NaCl is partly retained or at least not excreted with the urine. This fact became still more obvious on the next day, when with the breakfast 10 gm. of salt was given.

TABLE 2

Hour	Quantity of Urine (c.c.)	NaCl in %	NaCl in Gm.	Quantity of Water Taken (c.c.)
8–10	360	0.024	0.0864	400
10–12	580	0.12	0.696	400
12– 2	1020	0.20	2.04	900
2– 4	620	0.22	1.364	700
4– 6	540	0.14	0.756	800
6– 8	620	0.09	0.558	700
8–10	350	0.08	0.280	800
10– 8	2360	0.13	3.068	2000
	6450		8.8484	6700

Here we see that a small part of the NaCl is retained in the body, though it is seen that the kidney has not lost its power of concentration, but that, on the contrary, its concentrating function is excellent.

It would have been important to estimate the chlorine content of the blood. This could not have been done every two hours, but was done every day for a week. Bang's micromethod (50) was used.

Date	*Chlorine in %*	
12 April	0.61	
13 April	0.62	
14 April	0.60	
15 April	0.63	
16 April	0.69	10 gm. NaCl
17 April	0.68	
18 April	0.63	
19 April	0.61	

Here we see in first place that even when diet is very poor in salt there is a slight but distinct hyperchloraemia. The influence of 10 gm. of NaCl is still seen next day, when the greatest part has been eliminated through the kidneys. If these figures were submitted to one not knowing any clinical details of the case, his diagnosis would probably be "diabetes insipidus with hyperchloraemia."

Case II. A colonial officer, 48 years old, was treated in India for diabetes. He came with complaints of polyuria and polydipsia. The urine did not contain acetone or diacetic acid, but 2.4 per cent glucose with a diuresis of 9 liters. In this case the examinations could not be carried out every two hours, but were done with the urine of 24 hours. He received a mixed diabetes diet with 100 gm. bread and 6-8 gm. of NaCl daily.

TABLE 3

Date	Quantity of Urine (c.c.)	Chlorine in %	NaCl in Gm.	NaCl in Blood	Quantity of Water Taken (c.c.)	
3 May	8900	0.06	5.25	0.70	9000	
4 "	9100	0.03	2.73	0.68	8500	
5 "	9470	0.05	4.70	0.69	10000	
6 "	11200	0.06	6.72	0.74	12000	10 gm. NaCl extra
7 "	10800	0.05	5.40	0.72	11000	
8 "	9000	0.06	4.50	0.70	8550	

Here also we have a case of diabetes with hyperchloraemia. Not much influence is seen from the administration of 10 gm. of NaCl on the concentration of the urine. A remarkable fact is seen in the table.

When we know the quantity of NaCl ingested was approximately the same every day (and much attention was paid to this) then on May 3rd, 4th and 5th, 12.68 gm. of NaCl was eliminated in the urine; on May 6th, 7th and 8th, 16.62 gm. On the 8th of May, at which date diuresis has reached its ordinary height, the greatest part of the extra NaCl was still retained in the body, not in the blood, as is seen by the amount of NaCl in the serum. We are inclined to believe that it is retained in the tissues.

This corresponds with the theories of Veil (l.c.), Boenheim (51), and Meyer and Meyer Bisch (52) on the action of pituitrin. In this case it seemed of some interest to study the influence of pituitrin.

There was no reason to fear its influence on the diabetes mellitus. Not only have some authors recommended the use of hypophysis preparations in diabetes (Vigevani, 53), but diabetes mellitus is not considered as a contraindication for the use of these substances (Borchard, 54). It was observed that pituitrin had a marked influence on the excretion of water.

On May 9th the patient got four injections of 1 c.c. pituitrin.

TABLE 4

Time	Quantity of Urine (c.c.)	NaCl in %	NaCl in Gm.	NaCl in Blood	Quantity of Water Taken (c.c.)	
8–10	1080	0.05	0.540	0.69	900	10 o'clock 1 c.c. pituitrin.
10–12	360	0.13	0.468	0.68	400	
12– 2	220	0.12	0.264	0.69	300	2 o'clock 1 c.c. pituitrin.
2– 4	150	0.30	0.450	0.66	100	4 o'clock 1 c.c. pituitrin.
4– 6	0	....	....	0.66	300	
6– 8	420	0.41	2.722	0.67	300	8 o'clock 1 c.c. pituitrin.
8–10	200	0.38	0.76	0.68	150	
10– 8	1260	0.24	3.024	....	1200	
	3690		8.228		3650	

Though the influence of pituitrin is not so enormous as in some cases in the literature, it cannot be denied. It is remarkable that the NaCl content of the blood did not change. It seems to be possible in diabetes insipidus by administration of pituitrin subcutaneously dur-

ing a long time to obtain a temporary anuria (Gorke) and to obtain a normal NaCl content of the serum (Meyer and Meyer Bisch). It takes, however, many days of treatment before this is reached.

TABLE 5

Date	Quantity of Urine (c.c.)	NaCl in %	NaCl in Gm.	NaCl in Blood	Quantity of Water Taken (c.c.)	
8 Sept.	4750	0.24	11.400	0.54	5000	
9 "	5380	0.21	11.298	0.57	5450	
10 "	4250	0.22	9.350	0.57	4600	
11 "	6130	0.32	19.616	0.58	7000	10 gm. NaCl at breakfast.
12 "	4060	0.23	9.338	0.55	4120	

It would have been of interest to study the influence of thirst on metabolism; but as none of my patients could stand the headache they got in trying this, the experiments have not been continued.

Case III. A military officer presented a very serious case. When I saw him for the first time, diuresis was approximately 5 liters daily, with 3-7 per cent glucose, large quantities of acetone and diacetic acid.

TABLE 6

Hour	Quantity of Urine (c.c.)	NaCl in %	NaCl in Gm.	NaCl in Blood	Quantity of Water Taken (c.c.)	
8–10	600	0.21	1.26	0.56	720	10 o'clock 1 c.c. pituitrin.
10–12	450	0.23	1.03	0.58	300	
12– 2	400	0.21	0.82	11.56	540	2 o'clock 1 c.c. pituitrin.
2– 4	580	0.20	1.16	0.56	430	
4– 6	300	0.23	0.69	0.58	200	6 o'clock 1 c.c. pituitrin.
6– 8	420	0.24	1.01	0.56	700	8 o'clock 1 c.c. pituitrin.
8–10	680	0.20	1.36	0.56	420	
10– 8	1260	0.21	2.64	0.56	1400	

He died some months after the onset of treatment in coma diabeticum Here we have quite another type than in the two preceding cases.

Here we see a perfectly normal salt and water elimination. The amount of NaCl of the serum is normal, perhaps somewhat low. If we should feel inclined to compare this case to one of diabetes insipidus, it would be the hypochloraemical form. The difference from the normal is, however, too small to justify this diagnosis. Pituitrin had not the slightest influence on salt or water metabolism as is proved by the following data:

SUMMARY

There exist cases of diabetes mellitus with polyuria in which water and salt metabolism closely resemble the water and salt metabolism in the hyperchloraemic form of diabetes insipidus. There also exist cases in which such a resemblance cannot be demonstrated. Three case reports with metabolism findings are submitted in substantiation of these conclusions. It is not yet certain whether there exist cases of diabetes mellitus resembling the hypochloraemic form of diabetes insipidus.

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*STUDIES ON DISORDERS OF THE THYROID GLAND

III

FURTHER STUDIES ON THE PATHOLOGICAL AND CLINICAL SIGNIFICANCE OF DIFFUSE ADENOMATOSIS OF THE THYROID GLAND

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In a previous paper read before this society at its annual meeting last year I (1) drew attention to an interesting group of border-line nervous patients who present many difficulties in diagnosis and treatment and who complain of symptoms resembling in many ways mild chronic hyperthyroidism, incipient tuberculosis, neuro-circulatory asthenia, effort syndrome, psychasthenia, psychoneurosis, neurasthenia and other allied nervous states. I reported the peculiar symptomatology of this group of patients and the diagnostic findings which led me to think we were dealing with a mild chronic hyperthyroidism. I furthermore reported a considerable success obtained after partial thyroid resection. The pathological findings in the thyroid glands were striking and led me to believe that we were dealing with a hitherto unnoticed type of thyroid pathology giving rise to a latent chronic hyperthyroidism, a condition which I called "Diffuse Adenomatosis." I wish to describe in some greater detail the symptoms and pathology of these cases and to point out what I consider the clinical and pathological significance of this group of thyroid disorders.

I may review briefly the history, symptomatology and differential diagnosis of this group of patients in the hope that similar cases may be properly diagnosed and that more may receive the benefits of what seems to be promising therapy for some of them. These patients are mostly women between the ages of twenty and thirty with the following symptoms—asthenia, fatigueability, loss of weight and strength, nervousness of varying degrees, labile pulse with mild tachycardia, tremor, perspiration, vasomotor instability, mental depression and worry and often a slight

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elevation of temperature. It is not at all surprising that these patients suffer under a variety of diagnoses of which incipient tuberculosis, psychoneurosis and neurasthenia may be mentioned. In fact several of my patients had been under medical care for years and in several instances had been sent to tuberculosis sanatoria under the impression that they were suffering with tuber-

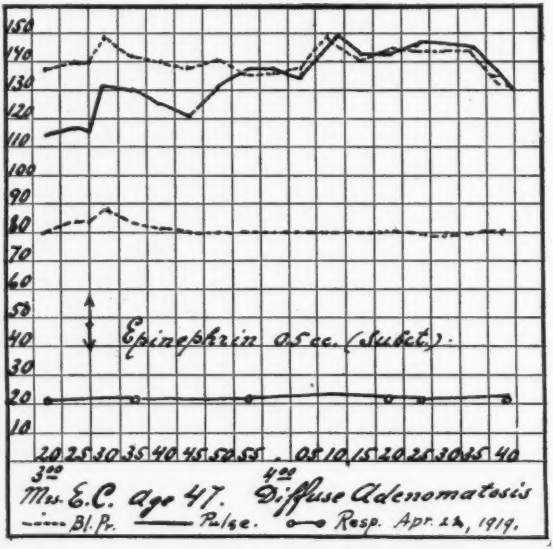

Fig. 1. Graphic chart of a moderately positive epinephrin hypersensitiveness test in a case of "diffuse adenomatosis", the thyroid gland of which is shown in microscopic section in Figs. 4 and 5. Note the early moderate rise of systolic pressure and the rather definite and sustained rise of pulse from 110 to the highest 144, reached about 40 minutes after the injection of 0.5 cc. epinephrin chloride. Very slight change in *diastolic* pressure. No change in respirations.

culosis, only to discover, after several months of rest régime, that there was little or no tuberculosis present. Others had wandered from physician to physician in search of relief and were finally diagnosed as psychoneurotics.

Speaking of clinical signs and findings, I may say that these patients do not present the well known cardinal signs of hyperthyroidism as we meet them in adenoma and in exophthalmic goitre. There is nothing peculiar noted about the eyes; the signs we find in oxophthalmic goitre are absent, the thyroid gland is often slightly or moderately enlarged, but may be neither visibly

TABLE I

Symptom chart of a positive epinephrin test obtained in the same patient whose chart is shown in Fig. 1. Note the early and sustained rise of pulse and the moderate rise of systolic pressure and the expression of signs and symptoms produced by the injection, such as increased throbbing, feeling of faintness, marked tremor, erythema, general trembling and vasomotor changes.

April 22, 1919. Pre-operative Epinephrin Hypersensitiveness Test. (Goetsch). Mrs. E. G. Age 47. Johns Hopkins Hospital Med. No. 41971.

Clinical Diagnosis: Moderate hyperthyroidism.

Operation: June 18, 1919. Double partial lobectomy of thyroid gland.

Pathological diagnosis: Diffuse adenomatosis.

Time.	Pulse	Resp.	B. P.	Clinical observations
3:20	114	20	137/80	Slight nervousness. Palms moist. No tremor
3:25	116		140/84	of extended fingers. Some throbbing over heart and back. No flush of face.
3:27½	Subcutaneous injection—Epinephrin 0:5 cc. (1-1000 sol.)			
3:30	132		148/88	Marked subjective symptoms. Feels faint. Lump in throat. Throbbing of abdominal aorta. Tremor in hands. Trembling.
3:35	130	20	148/88	Macular erythema of left side of face.
3:40	126		140/82	Patient complains of burning of face. Trembling
3:45	122		138/80	over entire body. Diffuse erythema of face. Nervousness increased.
3:50	132		140/80	"Face does not burn now." Erythema fading.
3:55	136	20	142/80	"Heart is beating harder."
4:00	136		140/80	
4:05	138		142/80	
4:10	148		145/80	
4:15	142		144/80	Symptoms gradually disappearing.
4:20	144	20	138/80	
4:25	144	20	138/80	
4:35	144		136/80	Tremor in hands not so marked as a half
4:40	132		134/80	hour ago.

Interpretation: A moderately positive hyperthyroid reaction as indicated subjectively by marked increase of symptoms and signs characteristic of hyperthyroidism and objectively by a sustained increase in pulse and systolic blood pressure.

nor palpably enlarged and, therefore, escapes notice as being the probable etiologic factor. When palpated the thyroid gland is fairly firm, elastic and does not show the presence of nodules as in adenoma; again thrills and bruits are absent. There may be a mild tachycardia; the pulse is labile but at rest may be normal. A fine tremor is usually present, and the hands are cold and clammy as a rule. The patient is underweight, looks run-down and asthenic and pallor is usually noted. Perspiration is also excessive.

The diagnosis of the true underlying condition in these patients is in part made by exclusion, in part by more direct evidence such as chronic symptomatology and a positive epinephrin test, to be mentioned again. The majority of my patients had had medical treatment over long periods of time, as much as several years in a few instances, with little or no benefit. This alone

makes me suspicious, since incipient tuberculosis and also various nervous states so often yield to rest, diet and medicines. The complaint is characteristic of a mild chronic hyperthyroidism, though to be sure, not pathognomonic of it. Finally I am able to demonstrate a hypersensitiveness of these patients to my epinephrin test (Fig. 1, Table 1), which gives such a typical response in hyperthyroidism. In pure tuberculosis my test is negative (fortunately for the differentiation of diffuse adenomatosis from incipient tuberculosis), and in the other allied conditions, such as effort syndrome, psychoneurosis and neurasthenia, the test is either distinctly atypical, does not give what I have described as a positive hyperthyroid response, or is entirely negative.

I should like to emphasize a few points in the history of these patients which help to differentiate the latter from cases of neuro-circulatory asthenia, psychoneurosis and neurasthenia. One often finds that in these conditions the complaint is variable and vague and dates far back into childhood. The onset of the trouble is very indefinite; in fact one is tempted to think that the condition is inherited, since it frequently begins in childhood, and one often finds that the parents are of nervous type. I am inclined to believe that we are dealing with a constitutionally inferior nervous system in some of the allied states. Hyperthyroidism or dysthyroidism (and under these I have grouped these cases of diffuse adenomatosis), usually has a definite starting point. The patient generally knows when her symptoms began and very often dates them from the time of puberty, whereas before that time she may have been in very good health and entirely well. The neurasthenic or psychoneurotic on the other hand often does not remember when she really felt well. The symptoms may begin after pregnancy and sometimes after an acute infection such as "flu" or pneumonia. Again, the complaints in hyperthyroidism are usually quite definite and characteristic, whereas in the allied functional nervous states the complaints are frequently varied and extremely vague.

Unfortunately, I am unable to report the metabolic rate determination in this series of patients, as most of them were observed previous to a year ago, at which time I was not determining metabolic rates as a routine in my thyroid patients.

However, after I first drew attention to this group of thyroid disorders, Woodbury (2) made a number of determinations upon this type of patient and found that the metabolic rate is not particularly increased, in fact it may be normal or only slightly abnormal. As I pointed out last year, I think Woodbury is correct in assuming that regardless of the normal metabolic rate these patients were suffering with hyperthyroidism. It would seem that the epinephrin test, which is more sensitive than the metabolic rate determinations, is positive in these individuals, though mildly so, and hence is in this group of more diagnostic value than the metabolic test. This finding is somewhat similar to that found in the quiescent phase of adenoma at which time the metabolic rate is found to be normal, whereas, since the hypersensitiveness of the sympathetic nervous system is a persistent characteristic, the epinephrin hypersensitiveness is even then positive.

Working on the assumption that these patients were suffering with some kind of chronic thyroid intoxication, on account of the characteristic symptomatology, the failure to gain after ordinary measures and the positive epinephrin test, I decided to resect the thyroid gland. Knowing that no harm would be done, I decided to operate with the full permission and understanding of both patient and physician. These patients were all too ready to undergo any measures at all, a fact which made it doubly necessary that operation should only be done as a last resort and after other measures had failed. Otherwise, I was well aware that needless operations would be done in patients not well chosen or properly diagnosed.

The thyroid gland is found to be slightly or not at all enlarged in "Diffuse Adenomatosis." It has the dark pink color of the hyperplastic gland. On palpation it is found to have a granular or lobulated feel, the consistency is slightly firmer than normal but definite nodules are not felt. The delivery of the thyroid lobe is sometimes difficult because of the periglandular adhesions which are frequently found. There is an increased vascularity; the cut surface tends to bleed rather profusely. There is a diminished amount of colloid in the gland, thus distinguishing it from the simple colloid goitre, and the consistency is not as firm as in exophthalmic goitre, nor is there the character-

istic lobulation seen in the latter. These changes are uniform throughout the entire gland.

Upon microscopic examination (Figs. 2, 3, 4) we find the striking and characteristic change to be a marked increase of interstitial cells scattered diffusely and in large numbers throughout the gland with an associated atrophy and almost complete disappearance in some areas of the colloid acini. The interstitial cells are readily recognized as being epithelial and not connective tissue or lymphoid cells by the fact that they possess a considerable amount of protoplasm and have a fairly large, round, vesicular nucleus with abundant chromatin granules. The cells have no definite arrangement, are present in large numbers throughout the gland, and by pressure cause atrophy of the true alveolar epithelial cells. Here and there abortive attempts at the formation of young, small alveoli are recognized, and occasionally large, clear cells with large nuclei are seen filling the spaces in these acini which are ordinarily occupied by the colloid. The appearance is one of desquamated cells arising from the epithelial alveolar cells lining these new-formed acini. Then again here and there hyperactive looking acini with little colloid, tall columnar lining cells and large, dense nuclei are seen. These have the appearance of exophthalmic goitre acini. They are few but striking in appearance and so different from the appearance of the majority of the acini, which are often separated from one another by an apparent invasion of the interstitial tissue, and are smaller than those in the normal gland, also much less numerous, and lined by flat, atrophic looking alveolar cells. In a few instances, lymphoid cell accumulations are seen, but these are readily distinguishable from the interstitial cells by their small pycnotic nuclei and lack of protoplasm.

These findings are the precise opposite of those found in colloid goitre, puberty hyperplasia and exophthalmic goitre, in all of which there is a conspicuous absence of interstitial cells, conditions none of which could possibly be confused with diffuse adenomatosis. On the other hand, the opposite might also be expected and is in fact found in diffuse adenomatosis, for as we have seen there is a marked increase in the interstitial cells with an atrophy and even disappearance of the colloid acini. As I have previously pointed out, in cases of adenomata, tumors

which are toxic and arise from individual groups or nests of interstitial cells, there is an associated atrophy and regression to form the simple colloid picture in the thyroid gland outside of the adenoma. This result may be analogous to the production of an inactive colloid gland by the experimental administration

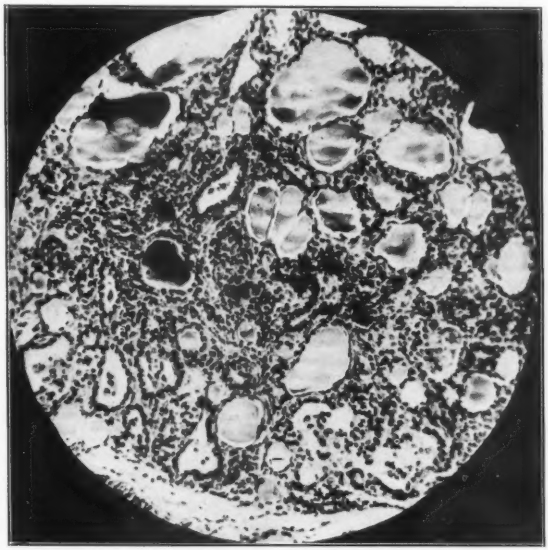

Fig. 2. Low power (Proj. oc. No. 2, Obj. 8 m.m. achromat. Camera length 28-in.) photomicrograph of section from thyroid gland of a woman of 47 years who had a chronic complaint lasting over several years, consisting of palpitation of the heart with paroxysmal attacks of tachycardia, weakness, nervousness with tremor, depressions and indigestion. No relief under prolonged medical measures. Chief findings were: no exophthalmos, slight enlargement of the isthmus of the thyroid gland, lateral lobes not palpable. No nodules, no bruits felt. Slight fine tremor of the fingers. Palms moist. Feet cold. Hypotrichosis. Reflexes at the knees active. General clinical findings were temperature 98 to 99.6. Pulse averages 70 when patient is calm and at rest, but frequently runs up to 110 and 120 with exertion or under emotion. Moderately active epinephrin hypersensitiveness test.

Operation June 18, 1919. Bilateral partial resection of the thyroid gland. Good post-operative recovery.

Note the abundance of interstitial cells separating the atrophic colloid acini. One sees in the midst of the interstitial tissue several new-formed acini, which are lined by tall columnar active-looking epithelial cells in sharp contrast with the low flat atrophic acini of the remaining thyroid gland.

of iodine or iodides to animals, such as the opossum (Bensley) and the dog and sheep (Marine). In the case of the adenoma the toxic material or possibly hormone is furnished by the cells of the adenoma, arising, as we believe, from the foetal cells of

Cohnheim; in the meantime there is no call for the secretion of the normal thyroid alveoli, which consequently atrophy and become inactive. The same atrophy and inactivity are found in the remaining colloid acini of the gland in diffuse adenomatosis, another indication by analogy that there is a hormone or toxic

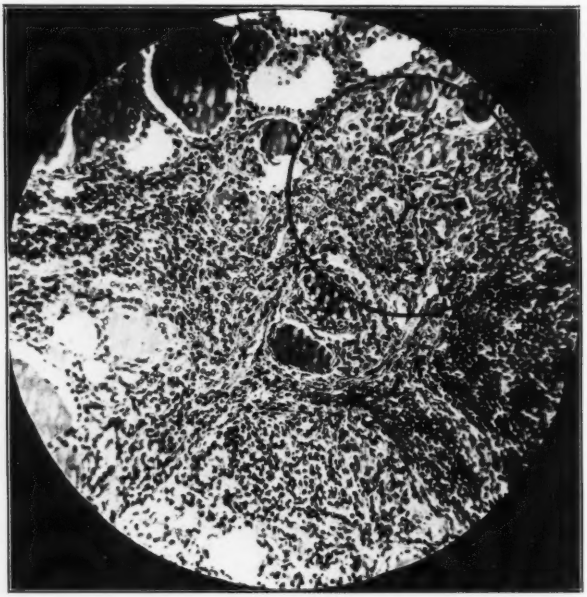

Fig. 3. Low power (Proj. oc. No. 2, Obj. 8 m.m. achromat. Camera length 28-in.) photomicrograph of section (5 m.m. thickness haematoxylin and eosin) from the thyroid gland of a young woman of 20 years, who complained principally of nervousness, worry, crying spells, trembling, dysmenorrhoea, weakness and loss of memory. The chief findings were absence of eye signs, slight uniform enlargement of the thyroid gland but without nodules or bruits. Slight tremor. Reflexes generally increased. Pre-operative epinephrin test definitely moderately positive.

Operation Nov. 29, 1915 by Dr. E. Goetsch. Partial resection of right thyroid lobe, excision of isthmus and small portion of left lobe. Very good recovery and marked post-operative improvement.

Note the great abundance of interstitial tissue, the lymphoid cell accumulation below and to the right, and the growth of cells in the indefinite acini in the midst of the interstitial tissue. Note also the relative absence of acini which are atrophic in appearance.

production of thyroid secretion on the part of the interstitial cells; otherwise why should the colloid acini atrophy? It is not pressure altogether, if at all, for I have found this atrophic colloid change even in the normal opposite lobe in cases of unilateral

adenoma. Another indication of the inactivity of the alveolar cells in both of these conditions is the almost complete absence of mitochondria (3) in the acinar epithelial cells. We know hyperthyroidism can be produced by adenoma, the cells of which I believe have the same origin as the interstitial cells in diffuse adenomatosis. Should we not expect, therefore, symptoms pro-

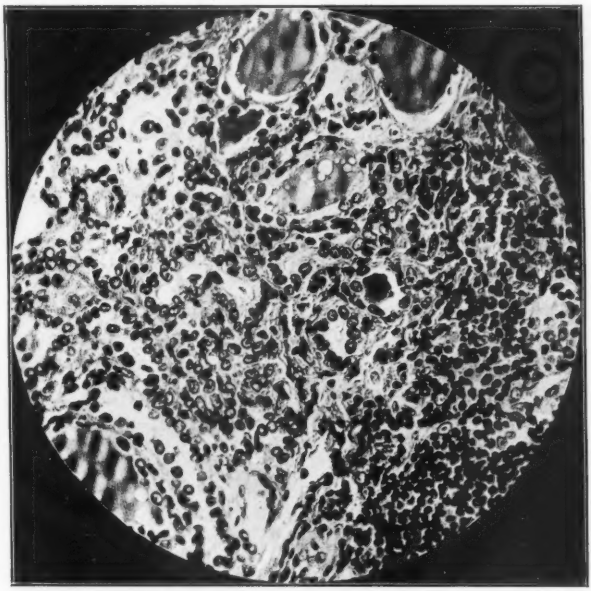

Fig. 4. High power (Proj. oc. No. 2. Obj. 4 m.m. apochromat. Camera length 28-in.) photomicrograph of area within the dark circle in Fig. 3. Note the distinct epithelial nature of the interstitial tissue in sharp contrast to the lymphoid cell accumulation shown in the right of the section. Note the abortive irregular new formed acini lined by the large protoplasmic cells and enclosed within the interstitial tissue. These newly formed acini appearing more active than the old atrophic acini of the original thyroid gland as shown at the upper and lower edges of the photograph.

duced by the secretion of the interstitial cells similar to symptoms found in cases of adenoma? Such I believe to be the case. As I had previously shown, the foetal adenoma (3, 4), before degeneration sets in, is histologically active in appearance, as indicated by the rich mitochondrial concentration in the cells. A similar richness of mitochondria is often seen in the interstitial cells of

diffuse adenomatosis. All these arguments are in favor of the view that we have in diffuse adenomatosis a toxic thyroid state, or a dysthyroidism depending for its symptomatology upon a marked hyperplasia and hyperactivity of the interstitial cells.

There are many points of similarity in the symptomatology of adenoma and diffuse adenomatosis, and why should there not be, if, as I believe, the intoxication depends upon activity of thyroid epithelium derived in both instances from the interstitial cells. The nervous and mental symptoms are much the same. Emotionalism, depressions, melancholia, impaired memory, and even talk of suicide are common complaints. The pulse is labile rather than accelerated, and vasomotor symptoms are frequently found together with increased perspiration. Excision of the adenoma is commonly found to relieve these symptoms, and just so resection of the thyroid gland, which reduces the amount of interstitial tissue in diffuse adenomatosis, has rendered patients of the latter group very much improved. To be sure, in diffuse adenomatosis, just as in exophthalmic goitre, one cannot remove all the offending thyroid tissue, hence the relief is not quite so striking in diffuse adenomatosis as in adenoma operation. In both instances the epinephrin test is moderately positive, and according to Woodbury (2), who has examined a series of these cases, the metabolic rate is not increased in diffuse adenomatosis, nor in the quiescent phase of adenoma. Pathological change, however, is always present and characteristically gives varied symptoms, according to the degree of activity at any one moment present. I think one cannot deny that there is a dysthyroidism present simply because the metabolic rate is not distinctly increased, for when a normal metabolic rate is established in certain adenoma cases, relief of symptoms follows only after excision of the adenoma.

I feel that we are dealing with a clinically very significant group of nervous people whose diagnosis and treatment in the past has been most obscure. There is doubtless a very considerable percentage of patients in the so-called borderline group of nervous disorders who belong to the sub-group of thyroid gland disorders which I have termed "Diffuse Adenomatosis." I feel that more of these cases will be recognized if the trouble is taken to follow the advice I have given as to the importance of a very

careful history of the complaint, the establishment of a beginning point of the trouble, the failure of general measures and the positive epinephrin response. I want to state most emphatically that I do not feel that the majority of so-called borderline cases such as described, are thyroid cases and should be subjected to surgical measures. I do, however, feel that a percentage of these are thyroid disorders, which can be reasonably readily recognized after the measures advocated, and that in my experience a very considerable success has been obtained in a small series of cases after partial resection of approximately three-fourths of each thyroid lobe.

Turning now again to the pathology of this interesting condition, I may recapitulate to say that in the development of the early foetal thyroid gland two epithelial elements are recognized: first, the alveolar or parenchymal thyroid cells which form the colloid acini characteristic of the thyroid gland, and, second, the undifferentiated or perhaps dormant epithelial cell-nests, the so-called foetal or interstitial cells which are found in the interstices between the acini of the gland. In the normal gland the acini are fairly regular and there is a small amount of interstitial tissue. In the pathological evolution of the gland to form the various types of goitre with which we are familiar, we find that the alveolar epithelium may regress or atrophy, the colloid spaces distend, apparent partial disappearance of interstitial tissue takes place, and we have the simple colloid gland (Fig. 5). In the more actively functioning conditions of the alveolar epithelium alone, leaving aside the interstitial cells, we find alveolar hypertrophy and hyperplasia, giving rise to hyperthyroidism in puberty hyperplasia, and finally also in exophthalmic goitre (Fig. 5). Turning now to the interstitial cells, we find that individual islands of these cells may give rise to the discreet encapsulated foetal adenoma (Fig. 5), which in turn gives rise to hyperthyroidism. If now the cellular stimulus, whatever it may be, affects uniformly and stimulates to overgrowth the interstitial cells everywhere in the gland, then we have finally the condition in which I have become greatly interested, namely, "Diffuse Adenomatosis" (Fig. 5). The alveolar epithelium here undergoes atrophy and regression and the thyroid intoxication, I believe, is due to overaction of the abundant interstitial tissue.

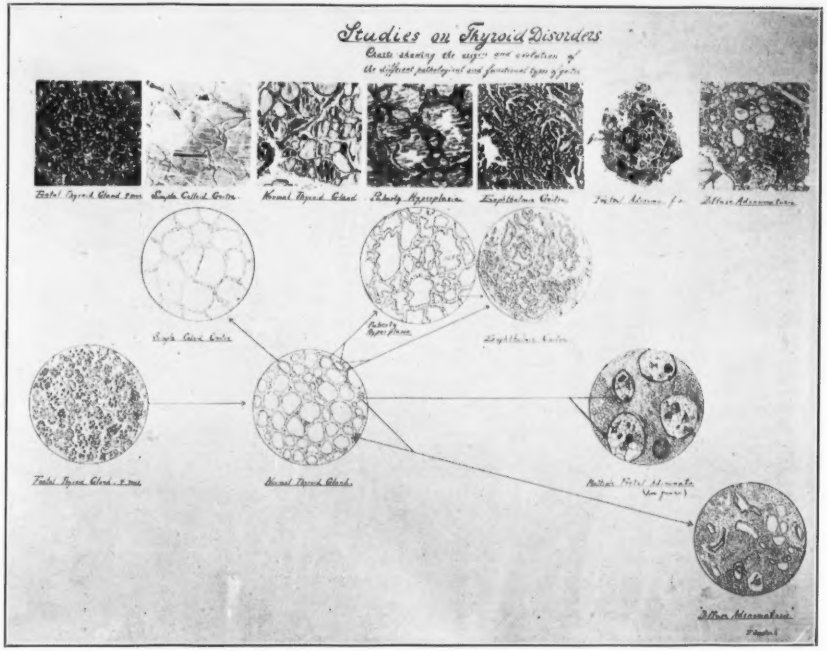
Studies on Thyroid Disorders
Chart showing the origin and evolution of the different pathological and functional types of goitre
Normal Thyroid Gland
Diffuse Adenomatosis

Fig. 5. Chart, semidiagrammatic, to show the derivation of the various pathological types of goitre from the two original epithelial elements in the thyroid gland, the acinar or alveolar epithelium and the interstitial or "foetal" cells. In the order of their activity and origin from the alveolar epithelium we have, first, the retrogressive relatively non-functioning simple colloid goitre, then the various degrees of function and hyperplasia as represented by the normal gland, puberty, hyperplasia and exophthalmic goitre. From the foetal or interstitial cells are derived the adenoma and finally, I believe, the "diffuse adenomatosis" as I have described it. The chart illustrates the derivation and the pathological position and significance of "Diffuse Adenomatosis" in the various groups of goitre.

So far as I know, what I have just elaborated is a new conception in the pathology of goitre. I feel, therefore, that we are dealing with a new group of individuals suffering with thyroid disorder. It is a significant group, clinically, both from the point of view of symptoms and treatment. From a pathological standpoint, I feel after a study of diffuse adenomatosis that we are dealing with a new pathological division of goitre which on microscopic section is just as characteristic as are puberty hyperplasia, adenoma or exophthalmic goitre. Whether the toxin produced is of the exact nature of thyroxin or not, or whether it is the same as that produced by adenoma, are questions which cannot be answered at the present time. Whether the disease should be considered hyperthyroidism in the same sense as adenoma or perhaps dysthyroidism consequent upon an altered secretion, are questions similarly unanswerable at the present time. That the secretion elaborated might be of a different character from that in the normal gland or in exophthalmic goitre is possible since the symptomatology is similarly somewhat at variance with these conditions. It may be that the different character of the disease is due to the fact that we are dealing with a chronic mild hyperthyroidism extending over some years of time, a fact which might readily give rise to a different syndrome than is found in the more acutely toxic thyroid states.

Realizing these facts, I feel that "Diffuse Adenomatosis" will be more often recognized by physicians who become acquainted with the symptoms, signs and diagnosis, particularly the differential diagnosis of this condition, and in a considerable number of instances relief may be offered by referring these sufferers to the surgeon for partial thyroid resection. Finally, I wish to emphasize the great care one must exercise in the diagnosis and treatment of these individuals in order not to be open to the serious criticism of performing futile thyroid operations upon nervous individuals wrongly diagnosed.

SUMMARY

Attention is drawn to that group of border-line nervous patients who present many difficulties in diagnosis and treatment and who complain of symptoms resembling, in many ways, mild chronic hyperthyroidism, incipient tuberculosis, neuro-

circulatory, asthenia, effort-syndrome, psychasthenia, psychoneurosis, neurasthenia and other allied nervous states. Some of these patients are suffering from a true thyroid disorder, perhaps dysthyroidism. There is no exophthalmos in diffuse adenomatosis. The thyroid gland is usually slightly enlarged, but does not present thrills and bruits. It shows a striking increase in the interstitial cellular tissue and atrophy, or partial disappearance of the colloid acini, a histological picture different from other forms of goiter. The patients react positively to the author's epinephrin hypersensitiveness test, whereas the metabolic rate may be within normal limits and therefore if the diagnosis of thyroid disorder were to be made purely upon increased metabolic rate, these patients would be overlooked. Treatment consists of resection of approximately three-fourths of each thyroid lobe. Considerable success has been attained in a small series of cases.

The term diffuse adenomatosis is restricted to the condition in which there is a general diffuse overgrowth of the interstitial epithelial cells as against the hyperplasia of the normal alveolar epithelium. The origin and nature of diffuse adenomatosis is a new conception in the pathology and clinical significance of thyroid disorders.

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ADRENAL FEEDING IN CONDITIONS OF HYPERTHYROIDISM*

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Certain derivatives of the entire adrenal gland produce physiological reactions which differ materially from those of commercial adrenalin (Parke, Davis & Co.).

The materials tested have been the nucleoproteins, the globulins and the coagulable albumens obtainable from aqueous extracts of this organ, and the non-coagulable "residue" of this extract. The latter is prepared as follows: After the precipitation by acetic acid of the nucleoprotein material from an aqueous extract of the hashed fresh (beef) adrenal glands, the filtrate is made slightly alkaline with NaOH and boiled to remove the alkali albumens; this filtrate is then again acidified and boiled to remove the acid albumens. There then remains a final dark-colored filtrate representing a non-coagulable somewhat hydrolyzed aqueous extract of the gland which, for lack of a better name, has been designated as the "adrenal residue." This is very rich in a pressor substance closely similar to epinephrin, but produces much more vigorous and lasting reactions, especially upon the stomach and pancreas, than do corresponding doses of adrenalin chlorid. An alcohol extract of the entire gland acts very similarly to this residue but not quite as intensively.

While studying these adrenal derivatives in comparison with adrenalin, it was found that they were all vasoconstrictors, apparently in proportion to their ephinephrin content, but differed decidedly from the latter material in that they all exhibited an inhibitory or "check" effect upon secretory activity, which was by no means in proportion to their epinephrin content. The results upon the pancreas, and particularly upon the stomach, were quite striking and seemed to indicate some clinical value in the adrenal nucleoprotein material which rather vigorously checks the total quantity of the gastric secretion and

* From the Johnston Livingston Fund for Experimental Therapeutics, Cornell University Medical College, New York City.

also decreases its acidity and more or less inhibits gastric peristalsis. Corresponding doses of adrenalin showed few or none of these "check" effects, which seemed to be brought about by stimulation of the functions believed to be mediated by the terminal filaments of the sympathetic in contradistinction to those of the autonomic system. Incidentally, it was found that the hypodermatic administration of the adrenal residue or of an alcohol extract of the gland (made by evaporating the alcohol and adding water until the epinephrin content was equivalent to that of the residue) produced anorexia, vomiting and extreme prostration, and the frequent repetition of the dose was liable to cause death.

Because these derivatives of the gland showed such striking inhibition of the alimentary tract, it was decided to test their effects upon the iodin content of the thyroid, especially as our experiments seemed to indicate a marked degree of physiological antagonism between derivatives of the thyroid and those of the adrenal glands.

It has long been known that the thyroid gland in Graves' disease, or conditions of hyperthyroidism, contains less than the normal amount of about 0.5 mg. of iodin per gram of gland substance. Moreover, the severity of the disturbance seems more or less to correspond to the degree of the thyroid's iodin loss, or to the degree of its inability to hold iodin. Consequently, any medicament which experimentally makes the thyroid gain in iodin should be of some therapeutic value.

Dogs were employed in the tests, and it was first learned that the extirpation of one thyroid lobe resulted, in untreated, healthy animals, in a gain of some 20 per cent to 30 per cent of iodin in the remaining lobe. The maximum gain seemed to be reached at the end of three or four weeks. Intercurrent malnutrition, or disease like mange, apparently lessened this gain. At the time of the second operation no gross change in the size of the thyroid lobes could be detected. Only those animals were employed which seemed in vigorous condition, and in which both lobes on inspection, appeared to be alike. Under ether, one lobe was then removed, trimmed, weighed and its iodin content determined by the Kendall methods (1). In

the preliminary tests the Riggs method (2) was used, but was later discarded in favor of the Kendall method which gives more uniform and trustworthy results. The same individual made all of these numerous iodin tests.

After excising one thyroid lobe from each of twelve selected animals, they were all then fed on a standardized diet consisting of cracker meal, evaporated milk, casein, lard, and bone ash, which was previously ascertained to maintain the nutrition and metabolism at a constant level. With this diet there was mixed daily for the first group of three, 0.016 gm. of adrenalin crystals (Parke, Davis & Co.); for the second group, 2 c.c. of the adrenal residue (Schieffelin & Co.), which contained an equal amount (0.016 gm.) of epinephrin—like material calculated by Folin's method (3); for the third group, 4 gm. of the adrenal nucleoprotein material (Schieffelin & Co.). This latter was a rather arbitrary dosage, as the nucleoproteins contain only faint traces of epinephrin. The fourth group of three dogs received only the standard diet and were retained as "controls." At the end of forty-five days (or considerably later than the period at which the maximum gain in iodin had previously been ascertained to take place in the single remaining thyroid lobe) the second thyroid lobe was excised from all the animals, weighed and tested for iodin. There were noted some slight variations in a gain or loss of gross weight in these (second) excised lobes; but the changes could be traced to differences in the trimming of foreign tissue or to the variations in the amount of blood. These variations, however, seemed to bear no relation to the changes in the iodin content, which were quite marked.

The thyroids of the "control" animals gained the normal average amount of about 30 per cent in iodin. Those fed the pure (commercial) crystals of adrenalin showed a slight increase over this, but so little that it was judged to come within the limits of error. In short, the results of adrenalin feeding were negative. But the group which was fed the adrenal nucleoprotein material showed a considerable increase, or an average gain in iodin of about 50 per cent. Those fed the adrenal residue exhibited the greatest gain, or on an average of 70 per cent.*

* A detailed statement of these experiments has been accepted for publication in the Am. J. Physiol. for March, 1922.

Although this series is rather too small to permit any very sweeping conclusions, the results agree so perfectly with many rather rough preliminary tests that there can be little doubt of some direct influence of the adrenal gland upon the thyroid. This influence seems to be exerted not so much by the active principle of the medulla or epinephrin, as by a combination of this with some other material, possibly from the cortex or from the entire organ, for the adrenal nucleoprotein material, with its mere trace of epinephrin, seemed to make the thyroid gain much more iodin than did a great deal larger dose of the adrenalin crystals. The latter, as previously stated, show a practically negligible effect. That this influence of the adrenal nucleoproteins, and especially of the adrenal residue, upon the thyroid is one of "check," or inhibition, seems very probable because, as mentioned previously, of what is known of the iodin content of the thyroid in health and in conditions of its excessive secretory activity or hyperthyroidism. The administration of iodin to these patients is generally contraindicated because of the well known danger of producing a violent exacerbation of the disease. Apparently, the hyperthyroid gland is unable properly to metabolize the iodin which usually reaches it, and when this amount is increased the epithelium seems to proliferate and break down and form little or no colloid material.

As yet, we can only speculate as to how this takes place. But the formulation of a theory is legitimate and a very necessary precedent to an exact knowledge of the process which seems to involve the involuntary nervous system and its functions.

The chief symptoms of *typical* hyperthyroidism, or conditions in which there is supposed to be a superabundance of the thyroid product, are referable to hyperactivity of the autonomic group of these nerves. Practically the only evidence of sympathetic involvement is the tachycardia, which is supposed to depend upon irritation or stimulation by the thyroid, of the cardio-accelerator or a sympathetic nerve. But the vaso-dilatation, the sweating and the signs of gastrointestinal activity are all evidences, not of sympathetic, but of parasympathetic or vagus, stimulation. Furthermore, in the typical cases, the tachycardia is something more than a mere increase in the rapidity of the heart action. There is a certain degree

of violence in the contractions which is very suggestive of vagus participation. Thus, clinically at least, the evidences of the disturbance in which the thyroid is believed to be abnormally active are all traceable to hyperactivity of the functions believed to be performed by the terminal filaments of the parasympathetic nerves.

Experimentally, the coagulable materials which can be isolated from the thyroid, when injected into animals, produce no appreciable immediate reaction. But the non-coagulable extracts, like one made with alcohol or a slightly hydrolyzed aqueous extract designated as the thyroid residue and prepared like the adrenal residue, are vigorous vasodilators and stimulants of the gastric and pancreatic secretions. These effects are produced apparently by direct stimulation of the terminal filaments of the parasympathetic or vagus group of nerves, which are believed in general to produce dilatation of blood vessels and increase in secretory activity (6). There are thus non-coagulable derivatives of the thyroid which excite immediate and definite physiological reactions.

Because these consist in stimulation of the functions believed to be performed by the parasympathetic or vagus portion of the involuntary nerves, and because this group shows marked activity in cases of typical hyperthyroidism, it is reasonable to believe that the thyroid product acts upon and through these particular nerve terminals and not through the sympathetic. Furthermore, because of the thyroid's well-known stimulating effect upon general metabolism, and because of the demonstrably stimulating effect of non-coagulable extracts of the thyroid upon some, if not all, parts of the parasympathetic system, the function of the product of the gland seems, broadly speaking, to be concerned with the production of energy in all the organs and tissues. In short, its function can be summarized as that of "drive."

Impulses which are antagonistic to those conveyed in the parasympathetic group of nerves seem to be discharged through the sympathetic terminals. Both are believed to be distributed to every organ, but to supply opposing impulses, or those which produce vasoconstriction and, in general, inhibition of functional activity. The action of the sympathetic nerves, with which the chromaffin tissue of the adrenal gland is so closely

associated, is thus apparently opposed to the thyroid-autonomic or vagus system, and can be summarized as that of "check."

As stated previously, derivatives of the entire adrenal gland like the nucleoprotein material, and especially the adrenal residue, apparently intensify this check of the nerve impulse much more vigorously than the epinephrin of the medulla. All of these derivatives contain more or less epinephrin. The latter, therefore, seems to be in the living animal only a stable component of a possibly larger and more labile product. However this may be, the stimulation or intensification of the check nerve impulse by these derivatives of the (entire) adrenal gland, like the stimulation of the drive by the thyroid, must be chemical. That is, the adrenal product after entering each cell must chemically restrain or "check" its metabolism, while the thyroid product on the other hand chemically accelerates or "drives" it. But each of these processes seems to depend upon the functional integrity of the nerve endings. For if these are lacking or are rendered functionless by poisons, as can be demonstrated in the stomach, the usual stimulation produced by the thyroid derivatives is absent. It is not as easy to destroy or paralyze the gastric sympathetic terminals and so demonstrate their importance for the action of the "check" derivatives of the adrenal. But these extracts have a stimulant effect upon the contraction of voluntary muscles, and this action is apparently exerted through the nerve end plate (5). The function of this organ can be completely abolished by fatigue and then the injection of the adrenal derivatives fails to excite a response. If, however, the fatigue is not complete, that is, if some response to electrical stimulation is still obtainable, the injection of the adrenal derivatives will immediately restore the vigor of the muscular contractions.

This fatigue experiment has considerable significance, not only in showing that the adrenal product probably acts through or upon the nerve terminals, but in suggesting the frequent origin of the hyperthyroid disturbance in a fatigue and consequent failure in functioning in the sympathetic or check mechanism. For if fatigue of the motor nerve end plate can abolish the influence of the adrenal product in voluntary muscles, fatigue of the involuntary or sympathetic nerve terminals in the viscera should interfere with or abolish their "check" influence. Be-

cause of the presence of epinephrin in all of these adrenal derivatives and its well known affinity for the sympathetic terminals, there is every probability that the normal adrenal product contains at least an epinephrin-like substance, and consequently acts through or upon the sympathetic endings and so intensifies or stimulates their apparent check function. Fatigue of the involuntary nerves, though it has not actually been demonstrated, undoubtedly follows the same laws which govern the fatigue and abolition of function in the voluntary nerve endings. If then fatigue should occur in the sympathetic terminals around the thyroid epithelium, the adrenal product could not act and the normal check upon the metabolic activity of the thyroid would fail. The result should be hyperthyroidism.

Clinically, these disturbances are so much relieved by rest and so much intensified by fatigue, that fatigue of the sympathetic or check portion of the involuntary nervous system seems to be the primary and most frequent cause of these functional thyroid disturbances. They also seem to follow infections, and hence there is every probability of the occurrence of a toxic damage or destruction of the restraining sympathetic terminals. Their total loss of function would cause the adrenal product or adrenal feeding to be useless. If only partial, the adrenal product or adrenal feeding would be more or less effective, as suggested by the partial loss of function by fatigue in the experiments with voluntary muscle. If the loss of function is not complete, the injection of the adrenal derivatives, as stated previously, restores the full vigor of muscular contractions.

To recapitulate this theory for hyperthyroidism and the influence upon the iodin content of the thyroid by feeding the adrenal nucleoproteins or the adrenal residue: The thyroid epithelium is supposed to receive a parasympathetic (vagus) nerve supply which accelerates or "drives" its metabolism of iodin, and a sympathetic which "checks" it. The product of the thyroid containing iodin, after its utilization (or any ingested thyroid material or ingested iodin), returns to its epithelial source, where it enters the epithelium only through the intermediation of the parasympathetic nerve terminals. The ensuing chemical processes, or metabolism into a normal thyroid product, requires the normal functionation of the sympathetic or "check" nerve terminals in the thyroid through which the

is high and especially when there are signs of excessive gastrointestinal activity, the nucleoprotein material with its low epinephrin content seems to be more valuable than the adrenal residue. The adrenal residue, with its high epinephrin content, on the other hand, seems valuable in the average case in which the blood pressure is low and the gastrointestinal activity not excessive. Although the thyroid product with its contained iodin is supposed to return to its source and not be destroyed or excreted, there ought theoretically to be some advantages in combining with the adrenal feeding the administration at the same time of small doses of iodin. Practically, it will often be noted that neither medicament alone will be as efficient as both together; but when taking iodin in any form, a patient with hyperthyroidism should always be warned that if the gland swells or "feels tight" the iodin should be stopped. If this gross change in the adrenal product alone can exert its restraint. If either the sympathetic terminals or the adrenal product fail, the thyroid's metabolism of iodin becomes defective or too rapid and hyperthyroidism is the result.

Of course, the most obvious criticism of this theory is that hyperthyroidism does not follow Addison's disease; but in this condition the sympathetic nerves are presumably intact and the adrenal product cannot be assumed to be the only material which affects the tropic functions of the sympathetic. Experimentally, the fact remains that feeding derivatives of the entire adrenal gland to dogs causes the animal's thyroid to gain noticeably in its iodin content. Why the feeding of one adrenal derivative should be more effective in causing the thyroid to gain in iodin than the feeding of another, is a matter for speculation. But, clinically, in cases of hyperthyroidism, when the blood pressure gland is neglected there is grave danger of an ensuing acute and often dangerous exacerbation of the hyperthyroidism. Very little iodin seems generally to be required. Three to five drops of the official tincture in a half glass of water once or twice a day is usually sufficient and may be too much.

The following case histories are illustrative.

CASE I. G. W., age 20, broker's clerk, after a prolonged period of hard work with late hours, was first observed in January, 1917, with typical exophthalmic goiter of three or four months' duration. There were: marked exophthalmos; considerable, pulsating, symmetrically

enlarged goiter; pulse rate, 120 to 130; blood pressure, 120; weight, 145 lbs.

On Feb. 2, 1917, under local anaesthesia, both inferior thyroid vessels were tied, and on Feb. 9th, both superior vessels and a portion of the upper ends of both lobes were at the same time excised.

In April, the evidences of hyperthyroidism, with the exception of the goiter and some exophthalmos, had practically disappeared. The pulse rate was 80, and the weight 165 lbs. In June, work was resumed, and later all the symptoms gradually returned.

Nov. 13, 1918. Under ether, two-thirds of each lobe was excised and all the vessels in sight were, of course, tied and cut. There was a somewhat stormy convalescence, and the patient left the hospital at the end of a month improved, but still with marked signs of hyperthyroidism.

Jan. 9, 1919, there was moderate exophthalmos; the goiter, just after operation imperceptible, was now noticeable; the pulse rate was 100 to 110; blood pressure, 160; weight, 134 lbs. Weakness and diarrhoea were the chief complaints. Two 1-grain tablets containing 10 per cent of the adrenal nucleoproteins were then given every two hours. This form of adrenal feeding apparently had an immediately beneficial effect upon the diarrhoea, and the patient began to gain weight, which gradually increased during January and February to 150 pounds. The blood pressure fell from 165 to 145, but the pulse rate continued from 110 to 120.

In March, 1919, the adrenal residue in 10-drop doses every two hours was substituted for the adrenal nucleoproteins, and during the next month the pulse rate decreased to an average, while quiet, of about 90. But there was still noticeable exophthalmos and a goiter which, in spite of the liberal excision in the second operation, was as large as at the beginning of the disease. Then iodin, in the form of 1-grain pills of iodid of iron, was given three times daily. Within a few days the general condition appeared practically normal, but the goiter was perceptibly larger and firmer. The iodid of iron was, therefore, ordered to be discontinued. Two weeks later this patient was found with a rather violent exacerbation of his hyperthyroidism, apparently due to the iodin, which had been continued in spite of directions to the contrary. There was a temperature of 102; the pulse rate was 150 to 160; the blood pressure, 160, and the sweating and diarrhoea had returned.

During the next two weeks with feeding the adrenal nucleoprotein tablets, which seem particularly beneficial for the cases with diarrhoea, the symptoms gradually improved. When the gastrointestinal disturbance had subsided, feeding with the adrenal residue was resumed in 10 or 12 drop doses every two hours.

On May 15th, the pulse rate was about 90, but irritable; the blood pressure, 140; and the exophthalmos and goiter, noticeable. The 1-grain iodid of iron pills were then given one daily, but at the end

of ten days, although the hyperthyroid signs had nearly disappeared, the goiter began to swell and was accompanied by a feeling of pressure in the neck. The iodin was, therefore, immediately stopped until the uncomfortable cervical sensation had disappeared, and the goiter felt soft. By a little cautious experimenting, it was finally found, after another two weeks of the feeding with the adrenal residue, that the 1-grain iodid of iron pill could be taken every second day with apparent great advantage and without any subsequent swelling and "tightening" of the goiter.

If the adrenal feeding were omitted for two or three days the goiter immediately began to enlarge and feel uncomfortable. Apparently, the iodid had to be accompanied with the adrenal feeding to insure progress, and during June it was found that the iodid could be taken daily. In July and August the combination of iodin and adrenal feeding gradually seemed to complete the cure of all the symptoms except the exophthalmos and the goiter. The latter, however, had entirely disappeared in October, and the following month there was no exophthalmos and the medication was omitted. In January, 1920, the weight had reached 170, and no abnormality other than the cervical scars could be detected. This patient has continued well.

Case II. Mrs. A. M., age 42, presented a typical case of rather severe exophthalmic goiter, with slight exophthalmos, and only a just perceptible and symmetrical, firm enlargement of the thyroid. There was some pigmentation of the skin, considerable emaciation, much nervous irritability and frequent bowel movements. The weight was 86 lbs., pulse rate was 110 to 120, and the systolic blood pressure was 215. This patient had been confined to bed with a general sedative treatment for several weeks. Jan. 18, 1916, two 1-grain tablets containing 10 per cent of the adrenal nucleoproteins were given every two hours with an almost immediate relief of the frequent bowel movements and a more gradual decrease in the tachycardia.

On Feb. 15, the pulse rate averaged about 90, the weight had increased to 92 pounds, and the systolic blood pressure had fallen to 150. The goiter was softer, but the exophthalmos, unchanged. Operation was declined, as the improvement seemed to promise a recovery.

In September, 1916, after a period of considerable comfort and apparently following a few weeks of strenuous work, there was an exacerbation of the hyperthyroidism which was accompanied by a systolic blood pressure of 210. Feeding for about three weeks with the adrenal nucleoprotein material again seemed to reduce this to between 140 and 150, and also all the other symptoms. At the same time, the weight increased. One-grain iodid of iron pills were then added, one daily, to the adrenal feeding, and at the end of the month practically all of the symptoms had disappeared. This patient, later, again relapsed and again improved, and operation under the circumstances seems to offer little hope of a permanent cure.

CASE III. F. N., age 38, a salesman, presented typical exophthalmic goiter of several weeks duration. March 10, 1921, moderate exophthalmos; considerable symmetrical goiter, circumference of neck 15½ inches; weight, 150 lbs.; pulse rate, 120; blood pressure (systolic), 160, were noted. He was given the 1-grain pills of iodid of iron, three daily, and warned to stop them if they caused swelling of the neck or any cervical discomfort. At the end of two days both the swelling and discomfort were noted, and, after discontinuation of the iodin, these signs soon disappeared.

March 22, 1921, the adrenal residue in 10-drop doses every two hours was then administered, with rapid improvement, especially in the subjective nervous irritability. The pulse rate was 90, blood pressure (systolic), 150; weight, 152 pounds. There was a slight decrease in the exophthalmos and goiter.

April 15, 1921, the patient returned after a month's rest in Atlantic City. The pulse rate ranged from 80 to 90; blood pressure was 145; weight, 155 pounds. One-grain iodid of iron pills once daily were now added to the adrenal residue, with warning as to the repetition of its possible ill effects.

May 23, 1921, gain much more than before taking the iodin was noted. The pulse rate was 82; blood pressure, 132; weight, 163 pounds. The circumference of the neck was 14¾ inches, showing marked decrease in goiter; the exophthalmos was less pronounced. The patient returned to work.

Sept. 12, 1921, the medication of the preceding month was discontinued and again marked and typical symptoms developed, but there was no loss of weight. Operation was advised, but at present the patient is again trying rest and the combination of iodid of iron with the adrenal residue.

SUMMARY

Experimentally, the feeding by mouth to dogs of derivatives of the entire adrenal gland, especially the adrenal nucleoproteins and a slightly hydrolyzed aqueous extract known as the adrenal residue, causes the animal's thyroid to gain from 50 to 75 per cent or more in its iodin content within a few weeks.

Feeding with corresponding amounts of adrenalin crystals is without appreciable effect upon the thyroid.

In conditions of hyperthyroidism the thyroid gland contains less than the normal amount of iodin per gram of gland substance.

The failure thus indicated of the thyroid to retain its normal amount of iodin apparently is due to a defect in the metabolism of iodin by the thyroid epithelium, and this defect is the probable biochemical cause of the disturbance.

The defect in the thyroid epithelial metabolism is theoretically dependent upon some preceding defect in the chromaffin, or automatic "check" system, and primarily begins in a failure in functioning of the thyroid terminals of the sympathetic nerves. It seems probable that the adrenal product acts through or upon these nerve terminals and, therefore, the functional integrity of these terminals is essential for the success of adrenal feeding.

Feeding with adrenalin, or the so-called active principle of the medullary portion of the adrenal gland, has no appreciable effect upon the iodin content of the dog's thyroid, and in human hyperthyroidism does not relieve the symptoms and may often intensify them (Goetsch test).

Three illustrative cases are cited.

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ADRENAL ENLARGEMENT IN RABBITS.*

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It has been observed on numerous occasions that the feeding of thyroid extract to animals causes an enlargement of the suprarenal glands, but hitherto no attempts to determine the mechanism of this action have been reported. The present study deals with the effect of various factors on the enlargement of the adrenals, and affords some evidence as to the mechanism of enlargement after feeding thyroid extract. We have also acquired evidence to show that enlargements of the adrenals following thyroid feeding, major emotions, and trauma, involve the cortex much more than the medulla of the gland, if, indeed, the latter is involved at all.

The first careful study of the relation between the adrenal and thyroid was that of Rudinger, Falta and Eppinger (1), who concluded that thyroid feeding stimulated the adrenals; similar results were reported by Kostlivy (2). Schafer (3) states that "It may be assumed that the secretion of the thyroid in exophthalmic goiter acts as a direct stimulant to the suprarenal capsules, causing them to yield adrenalin to the blood in larger quantity; a result which is also obtained by thyroid feeding."

After intravenous injections of thyroid extract, Ott and Scott (4) found an increase in the adrenalin content of the blood in experimental animals, but they were also able to obtain a similar result by injecting other organ extracts. Gley and Quinquaud (5) carried out similar experiments from which they concluded that intravenous injections of relatively large doses of extracts of thyroid and other glands (pancreas and liver) increased the epinephrin content of the blood. However, it has been pointed out by Stewart and Rogoff (6) that such extracts lower the blood pressure. Consequently, the rate of blood flow through the gland is diminished with resulting concentration of epinephrin in the adrenal vein. Iscovesco (7) found hypertrophy of the heart, thyroid, adrenals, kidneys, testes, ovaries and uterus after injections of thyroid extract.

R. G. Hoskins (8) fed guinea pigs desiccated thyroid gland substance from birth and found that the adrenals of eighteen animals so fed weighed 0.059 gm. as contrasted with 0.047 gm. in eighteen control

* We wish to express our thanks to Dr. L. H. Newburgh for his suggestions and help during this work.

animals of equal age and weight. Later E. R. Hoskins (9) studied the relation between thyroid feeding and the growth of various organs in albino rats and found a distinct increase in the relative size of the adrenals of all thyroid-fed groups. He found the reaction relatively more marked in males, in which sex the gland is normally lighter.

Herring (10) fed rats fresh minced ox thyroid mixed with bread in milk and found that both the cortex and medulla participated in the general adrenal enlargement which resulted, but that the enlargement of the cortex was relatively somewhat greater.

Kuriyama (11) fed rats a dog-biscuit-lard-thyroid mixture in quantities containing 1.0 gm. of thyroid per day for four days and found that the epinephrin content of the adrenals remained constant. The determinations were made by the Folin method.

Stewart and Rogoff (12) have concluded that the entire liberation of epinephrin is controlled by the sympathetic, as section of this nerve above the diaphragm abolished the spontaneous secretion, whereas section of the splanchnic alone did not entirely prevent the liberation of epinephrin. With this in view, we were careful in the experiments recorded below to destroy the adrenal innervation completely. Cannon (13) has shown that many factors cause a secretion of epinephrin, especially the major emotions, pain, and asphyxia, and that removal of the adrenal glands abolishes the effects obtained from such stimulation. Our experiments show that in rabbits, at least, the endocrine mechanism is distinctly labile and that extensive experimental procedures would be sufficient if continued to cause an enlargement of the adrenals in this animal.

METHODS AND RESULTS

Rabbits exclusively were used in this work. At the beginning of each experiment the animal was weighed and a serial number tatooed on the ear. This is a very convenient and rapid method of marking animals and, so far as we know, has not been described. India ink is used. A clean pen is dipped in the ink and the number written on the ear by a series of dots just piercing the skin. We have found this method to leave numbers legible for months.

A few animals died from intercurrent infections or other causes as noted in the protocols, but the majority were killed by a blow on the head. Immediately after death the final weight was recorded. In every case the adrenals were removed at once, carefully dissected free of fat, weighed on an analytical balance, bisected, the cortex measured, and the glands preserved in formalin. For histologic study specimens were embedded in paraffin and stained with haemotoxyline and eosin. The necropsy was completed by examination of other organs in the gross and weighing the heart and kidneys. The former was washed free from clots before weighing.

A control group of fourteen rabbits received the same general care and was kept under conditions approximately the same

as were the experimental groups. The average weight of the animals in this group was 1732 gm. The average adrenal weight was 294 mg. or 169 mg. per kilo and the average width of the adrenal cortex was found to be 1.8 mm. (Table 1).

Desiccated gland substance* was fed to a group of 15 rabbits. The thyroid preparation was mixed with sugar of milk, and put up in gelatin capsules. Each day one capsule was forced well down the throat by a short piece of small, soft rubber tubing. The thyroid dosage and the complete protocols are condensed in Table 2. The average weight of the animals of this group at the beginning of the experiment was 1812 grams and the average weight at the end was 1324 grams. The average weight of the adrenals was 444 mg. or 245 mg. per kilo of the original weight. Compared with the control series it will be seen that the adrenals of this group showed a definite increase in weight averaging 76 mg. per kilo, an enlargement of 45 per cent over the normal. Neither the heart nor kidneys showed comparable enlargement, although the hearts of the thyroid fed series were slightly heavier than those of the control group, averaging 2.7 gm. per kilo, as compared with 2.5 gm. per kilo in the control series. The average weight per kilo of the kidneys of the thyroid fed series was 6.2 gm.; that of the control group, 6.6 gm. per kilo.

The adrenal cortices of the thyroid fed series measured 2.3 mm., an increase of 0.5 mm. or 21 per cent over the normal controls. It is evident, therefore, that a great part at least of the increased adrenal weight can be attributed to cortical enlargement.

During the thyroid feeding a progressive enlargement of the adrenals was evident. The adrenals of four rabbits (Nos. 1, 3, 4, and 6), which received thyroid for less than 30 days, averaged 364 mg. or 244 mg. per kilo; those of three rabbits (Nos. 15, 11, and 14), which received thyroid for from 30 to 50 days, averaged 401 mg. or 262 mg. per kilo; those of three rabbits (Nos. 8, 19, and 17), which received thyroid for from 50 to 80 days, averaged 471 mg. or 260 mg. per kilo; and those of four rabbits (Nos. 10, 16, 12, and 13), which received thyroid for from 80 to 100 days, averaged 518 mg. or 273 mg. per kilo. For some reason (possibly a primary endocrine disturbance) rabbit

* The thyroid used was prepared and furnished by Parke, Davis & Co., for experimental work.

TABLE 1. NORMAL CONTROL SERIES.

No.	Sex	Best Weight Gm.	Final Weight Gm.	Heart Weight Gm.	Kidney Weight Gm.	Adrenal Weight Mgm.	Adrenal Weight per Kilo Best Weight Mgm.	Adrenal Cortex Width Mm.	Mode of Death
N	—	1720	1720	—	—	315	183	1.8	Killed by blow.
C	—	1506	1506	—	—	227	150	1.5	Bled from carotid.
5	—	1324	1324	3.5	7.0	222	167	—	Killed by blow.
24	♂	1531	1040	3.7	12.9	230	150	1.3	Died—Cause?
A25	—	1520	1270	4.2	11.0	215	169	—	Died—Pneumonia.
29	♂	1993	1993	4.2	10.2	350	175	1.8	Died—Peritonitis.
40	—	2053	2053	5.4	11.6	340	165	1.8	Bled from carotid.
42	—	2071	2071	4.9	12.7	400	193	—	Bled from carotid.
43	—	1230	1230	3.5	10.0	195	158	1.8	Killed by blow.
47	—	1438	1438	4.5	13.0	275	191	1.8	Died—Pneumonia.
55	♀	2083	2083	6.3	15.4	470	225	—	Bled from carotid.
56	♀	2064	2064	4.6	13.5	342	165	2.0	Bled from carotid.
57	♂	v 1849	1849	3.6	12.0	225	121	2.0	Bled from carotid.
58	♀	1870	1870	3.5	10.7	310	165	2.3	Bled from carotid.
Average		1732	1686	4.3	11.6	294	169	1.8	

TABLE 2. THYROID FED SERIES.

No.	Sex	Best Weight Gm.	Final Weight Gm.	Heart Weight Gm.	Kidney Weight Gm.	Adrenal Weight Mgm.	Adrenal Wt. per Kilo Best Weight Mgm.	Adrenal Cortex Width Mm.	Total Thyroid Fed Mgm.	Days Fed	Mode of Death
1	—	1570	1277	5.0	10.0	205	130	1.5	14	6	Killed by blow.
3	—	1400	1187	4.8	15.0	427	305	2.0	20	26	Died—Cause?
4	—	1490	1150	4.0	—	485	325	2.8	20	28	Killed by blow.
6	—	1550	1400	4.3	8.0	339	216	1.8	21	30	Killed by blow.
8	—	2087	1183	4.0	9.7	355	170	—	85	61	Died—Cause?
10	♀	2762	2611	7.0	18.5	665	240	2.3	164	81	Killed by blow.
11	—	1545	970	5.0	8.8	335	217	1.5	75	54	Dead—Caseous pneumonia.
12	♀	1930	1022	5.0	13.5	455	235	2.0	205	91	Died—Pneumonia.
13	♀	2090	1560	6.4	13.5	445	212	2.5	205	91	Killed by blow.
14	—	2032	1170	5.4	14.3	600	295	2.7	77	55	Died—Cause?
15	—	1545	836	3.9	8.1	272	176	1.8	53	38	Died—Lay on side. Heart occasionally irregular. Emaciated.
16	♀	1875	1691	5.0	14.5	760	405	3.5	165	81	Killed by blow.
17	♀	1690	944	5.0	10.0	485	286	2.2	148	79	Died—Cause? Very thin. Hair falling out.
18	♂	1885	1678	5.7	12.5	265	140	2.0	165	81	Killed by blow.
19	♂	1729	1186	5.0	12.8	575	332	3.5	143	78	Very weak. Killed by blow. Liver congested. Heart flabby.
Aver.		1812	1324	5.0	12.0	444	245	2.3	104	58	

No. 18 failed utterly to respond and both its absolute and relative adrenal weights were distinctly less than the averages for the control series. Consequently, it was not included in the last group. This progressive increase in adrenal weight is graphically represented in Fig. 1.

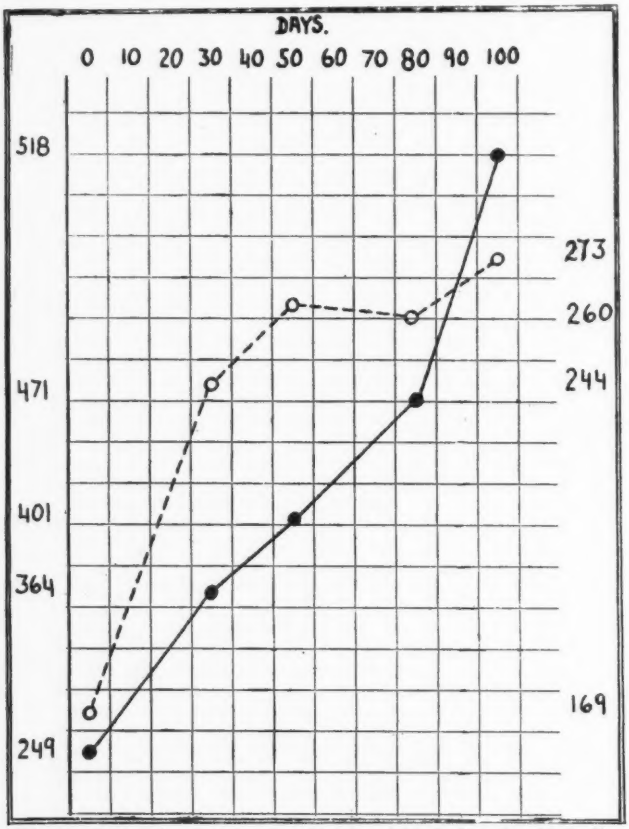

Fig. 1. Progressive increase in adrenal weight during thyroid feeding of rabbits. Heavy line and figures at left represent absolute adrenal weights; dotted line and figures at right represent adrenal weight per kilo.

None of the adrenals of the thyroid fed series showed any striking histologic changes.

In order to determine what effect, if any, the splanchnic nerves had in the production of adrenal enlargement, two groups

of animals were studied. In each group the splanchnic innervations of both adrenals was sectioned with aseptic precautions under ether anaesthesia.*

The operation was performed through an incision in the anterior abdominal wall. The nerves were cut as close to the diaphragm as possible and in each case at least 0.5 cm. of nerve was destroyed. The difficulties of this operation in rabbits are not great on the left side; on the right, however, the gland and nerve lie posterior and in intimate relation to the vena cava and hepatic ligaments. In every case care was taken to dissect the connective tissue immediately surrounding the glands in order to be certain that every path of communication was cut. The gland itself was handled as little as possible and in no case was obvious injury done to it. The skin and fascia of the anterior abdominal wall were sutured with chromic catgut, usually in two layers. At necropsy no uncut fibrils of nerve were ever found. After the skin wounds had healed (generally in about ten days) one group of splanchnectomized animals was fed desiccated thyroid extract by forcing thyroid filled gelatin capsules down the throats with a soft rubber tube as already described. A control group of animals similarly operated upon received the same general care and was kept under conditions approximately the same as the thyroid fed group.

In the splanchnectomized control group the average weight of the animals was 1914 gm. at the beginning and 1544 gm. at the end of the experiment. The adrenals of the group averaged 482 mg. or 245 mg. per kilo of initial weight. It is to be noted that compared with the normal control series these adrenals averaged 76 mg. per kilo or 45 per cent heavier, an increase identical with that which was found after thyroid feeding. It is of interest also that the heart weight in the splanchnectomized control group was 2.7 gm., and the kidney weight was 6.2 gm. per kilo., corresponding exactly with the weight per kilo of these organs in the thyroid fed series (Table 3).

Thyroid feeding in the second splanchnectomized group of seven rabbits was continued for periods varying from 7 to 66 days. In this group the average weight of the animals at the beginning was 2722 gm. and at the end it was 1856 gm. The

* We wish to express our thanks to Nina A. Squier for assistance in anesthetising the animals.

TABLE 3. SPLANCHNECTOMIZED CONTROL SERIES.

No.	Sex	Best Weight Gm.	Final Weight Gm.	Heart Weight Gm.	Kidney Weight Gm.	Adrenal Weight Mgm.	Adrenal Weight per Kilo Best Weight Mgm.	Adrenal Cortex Width Mm.	Days After Operation	Mode of Death
64	♂	1966	1528	4.0	8.0	540	274	1.8	27	Killed by blow.
60	♀	1600	1513	4.0	10.0	290	187	2.0	44	Killed by blow.
63	♂	1932	1932	5.7	14.0	315	163	1.8	42	Killed by blow.
86	♀	1925	1034	5.7	12.0	385	200	—	33	Dead—Cause?
89	♀	1620	1330	6.0	12.0	270	166	2.0	37	Killed by blow.
93	♂	2240	2100	5.9	14.7	765	341	3.0	47	Killed by blow.
95	♂	2120	1370	5.5	13.2	815	384	—	23	Dead—Cause?
Average		1914	1544	5.2	11.9	482	245	2.1	36	

TABLE 4. SPLANCHNECTOMIZED THYROID-FED SERIES.

No.	Sex	Best Weight Gm.	Final Weight Gm.	Heart Weight Gm.	Kidney Weight Gm.	Adrenal Weight Mgm.	Adrenal Wt. per Kilo Best Weight Mgm.	Adrenal Cortex Width Mm.	Total Thyroid Fed Mgm.	Days Fed	Days After Operation	Mode of Death
28	♂	2674	1495	6.2	12.7	705	263	3.2	35	7	28	Died—Cause?
31	♂	2703	1839	5.5	15.5	835	308	3.6	80	17	38	Died—Pneumonia.
36	♂	3583	1974	9.0	14.9	680	189	—	185	42	75	Killed by blow.
33	♂	2746	2030	7.5	12.3	995	362	3.0	675	66	88	Killed by blow.
71	♂	3317	2265	8.2	16.5	865	260	3.9	200	20	32	Killed by blow.
73	♂	2450	2080	7.5	12.0	690	281	—	1599	65	75	Killed by blow.
84	♀	1580	1316	—	—	245	165	2.0	460	27	37	Died—Cause?
Aver.		2722	1856	7.3	13.9	716	261	3.1	762	35	53	

average adrenal weight was 716 mg. or 261 mg. per kilo. The hearts of this group averaged 2.6 gm. per kilo, and the kidneys averaged 5.1 gm. per kilo. The adrenal cortices averaged 2.8 mm. in width (Table 4).

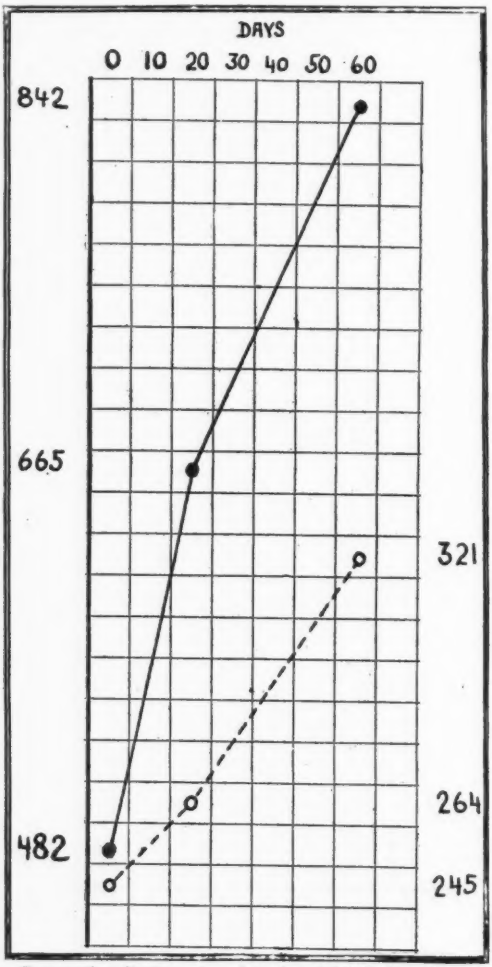

Fig. 2. Progressive increase in adrenal weight during thyroid feeding of rabbits in which the splanchnic innervation of the adrenals had been sectioned. Heavy line and figures at left represent absolute adrenal weights; dotted line and figures at right represent adrenal weight per kilo.

The same progressive increase in adrenal size during the period of thyroid feeding was noted in this group as in the unoperated thyroid fed rabbits. The adrenals of rabbits Nos. 28,

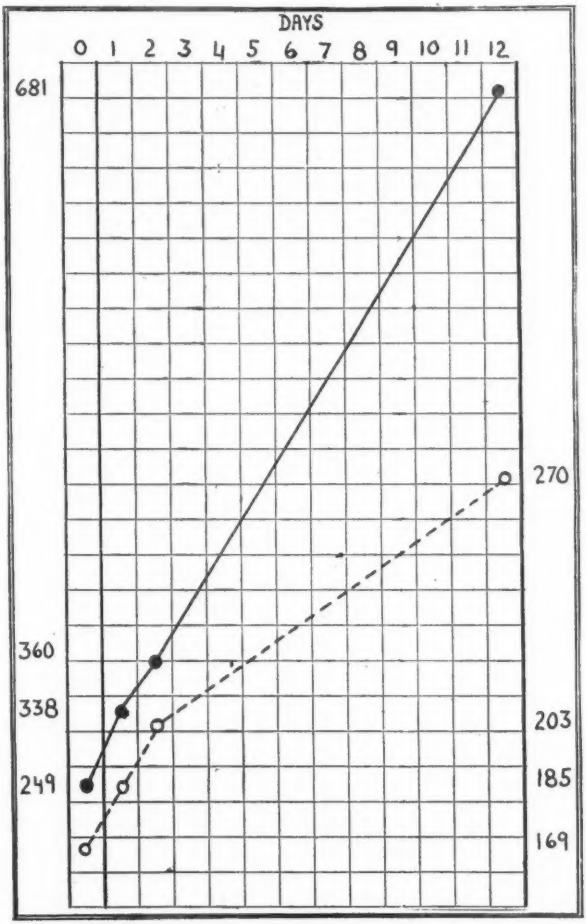

Fig. 3. Progressive increase in adrenal weight resulting from continued trauma or shock. Heavy line and figures at left represent absolute adrenal weights; dotted line and figures at right represent adrenal weight per kilo.

31, 71, and 84, fed thyroid from 7 to 27 days, averaged 665 mg. or 264 mg. per kilo; adrenals from rabbits 33 to 73, fed thyroid

TABLE 5. TRAUMATIZED SERIES.

No.	Sex	Weight Gm.	Heart Weight Gm.	Kidney Weight Gm.	Adrenal Weight Mgm.	Adrenal Weight per Kilo of Body Wt. Mgm.	Adrenal Cortex Width Mm.	Mode of Death
20	♂	1776	—	—	310	174	2.0	Operated upon—Died on table.
21	♂	1908	—	—	235	123	—	Operated upon—Died on table.
22	♀	1385	—	—	330	238	2.7	Operated upon—Died on table.
23	♂	1385	—	12.5	525	378	2.3	Fight—Died 10 days later.
26	♂	1765	4.2	8.5	360	203	—	Operated upon—Died 2 days later.
34	♂	2746	6.3	14.3	780	284	2.9	Fight—Died 12 days later.
35	♂	3383	7.4	15.5	740	218	1.8	Operated upon—Died 12 days later.
38	♂	2340	6.0	11.2	480	205	2.1	Operated upon—Died on table.
		2086	5.9	10.3	470	228	2.3	

TABLE 6. SERIES TUBED WITHOUT THYROID.

No.	Sex	Original Weight Gm.	Final Weight Gm.	Heart Weight Gm.	Kidney Weight Gm.	Adrenal Weight Mgm.	Adrenal Weight per Kilo of Original Weight Mgm.	Days Tubed	Mode of Death
96	♀	2330	2190	5.0	10.4	1065	457	30	Killed by blow.
97	♀	2295	2335	5.9	12.5	460	197	30	Killed by blow.
98	♂	2135	2125	3.8	11.1	300	140	30	Killed by blow.
99	♀	2155	2340	7.4	12.6	590	252	30	Killed by blow.
100	♀	2145	2030	5.0	10.4	515	240	30	Killed by blow.
		2212	2204	5.7	11.4	586	257	30	

65 days, averaged 842 mg. or 321 mg. per kilo (Fig. 2). No important histologic changes were found in the glands of either of the groups of splanchnectomized animals. These results would indicate that, subsequent to the trauma and shock of operation, there is a definite adrenal enlargement quite comparable to that following administration of thyroid extract by the method described. Furthermore, when thyroid extract is fed to such traumatized rabbits there is still greater increase in the size of the adrenals in spite of the fact that the nerve supply to the glands has been sectioned.

It appeared evident from the results obtained in the splanchnectomized control group that simple trauma and shock were sufficient to produce definite adrenal enlargement. Consequently, it seemed advisable to study a group of animals from this standpoint alone. Four animals (Nos. 20, 21, 22 and 38) died on the operating table while splanchnectomy was being done and the adrenals of these averaged 338 mg. or 185 mg. per kilo; very slightly heavier than the average weight per kilo of the normal adrenal series. One animal (No. 26) died two days after operation and its adrenals were found to weigh 360 mg. or 203 mg. per kilo. No. 35 died 12 days after operation; Nos. 23 and 34 died about ten days after fights in which they were severely injured. The adrenals of the last three rabbits averaged 681 mg. or 270 mg. per kilo (Table 5). Again in this series a progressive enlargement of adrenals was noted. The longer trauma had been acting, the larger were the adrenals found to be. A graphic representation of this result will be found in Figure 3. The severity of the trauma unquestionably would also be a factor, but in the cases cited the trauma in each case was approximately of the same intensity—sufficiently great to result in death.

Since shock is sufficient to produce adrenal enlargement and since the adrenal enlargement of the untraumatized thyroid fed rabbits was no greater than in the splanchnectomized control group, the question naturally arose whether simple intubation with empty capsules would not cause as much enlargement as was produced by the feeding of small quantities of thyroid. Consequently, five rabbits were selected averaging 2212 grams in weight and for thirty days an empty gelatin capsule was daily forced down the throat of each with a soft rubber tube exactly as was done with the thyroid fed rabbits. At the end

of the period the animals were killed by a blow on the head. The average adrenal weight of this group was 586 mg. or 257 mg. per kilo. Consequently, intubation alone is sufficient to cause a definite adrenal enlargement. Comparing the adrenal weights of this group with the average adrenal weights of rabbits Nos. 3, 4, 6, and 15, which were fed thyroid for 30 days, it will be seen that the adrenals of the thyroid fed animals averaged 282 mg. per kilo or 25 mg. per kilo heavier than the adrenals of the tubed controls. It is evident, therefore, that trauma or stimulation will produce an adrenal enlargement of apparently the same kind as that resulting from thyroid feeding, but that the same trauma or stimulation plus thyroid will produce still greater enlargement (Table 6).

DISCUSSION

The results of this work seem to point definitely to a thyroid adrenal relationship. Cannon and Cattell (14) have shown that epinephrin causes an action current in the thyroid and that a similar result can be produced by stimulation of the splanchnic nerve. Other workers, as has been already mentioned, have found adrenal enlargement when thyroid gland substance was fed in a more natural manner, and our results show that the adrenal enlargement from thyroid capsule intubation is greater than that from simple intubation over a corresponding period of time. It seems very probable that any trauma or nervous stimulation of sufficient intensity results in increased secretion of thyroid hormone which in turn produces enlargement of the adrenal cortex. An increased width of adrenal cortex in experimental hyperthyroidism has been previously noted (15). We have shown that this enlargement does not take place as a result of stimuli passing along the splanchnic innervation of the adrenal glands for the enlargement occurs just as readily in animals in which these nerves have been cut. Consequently, it seems probable to us that the thyroid hormone acts directly upon the adrenal cortex.

Herring (16) did thyroidectomies on rabbits and found in a control group in which the thyroid gland was merely exposed that the adrenals averaged 200 mg. per kilo, while in a similar group in which thyroidectomy was actually performed the adrenals averaged 172 mg. per kilo. This last weight is practically the normal weight (169 mg. per kilo.). Viewed in the light of our

studies this effect is exactly what would be expected. In Herring's control group the adrenal cortex was stimulated by the thyroid hormone liberated as a result of trauma, while in the thyroidectomized group the adrenals were of normal size because there was no thyroid available. In both groups he found the adrenals to have practically the same epinephrin content.

Many attempts to demonstrate thyroid-adrenal interrelation have been made through quantitative determination of epinephrin, but the majority of these investigations have omitted the adrenal cortex from consideration. The results have been conflicting and in general negative. On the other hand, our evidence as well as that of other workers seems to point conclusively to a definite relationship between the thyroid hormone and the adrenal cortex.

SUMMARY

1. The adrenals of rabbits fed desiccated thyroid extract by the method of intubation described averaged 245 mg. per kilo., as compared with 169 mg. per kilo. in control rabbits. The enlargement was greatest in those animals fed thyroid over the longest period.

2. The adrenals of rabbits which had recovered from an operation in which splanchnic nerve supply to these glands had been sectioned averaged 482 mg. or 245 mg. per kilo.

3. The adrenals of rabbits which had recovered from an operation in which the splanchnic nerve supply to these glands had been sectioned and which were then fed desiccated thyroid gland by the method of intubation described averaged 716 mg. or 261 mg. per kilo. The enlargement was relatively greater in the adrenals of animals which had received thyroid over the longest period.

4. The adrenals of rabbits which had received traumatization sufficient to result in death average 470 mg. or 228 mg. per kilo. The enlargement was relatively greater in the adrenals of animals which had been subjected to trauma over the longest period.

5. The adrenals of rabbits mildly traumatized or stimulated by the intubation method used in feeding thyroid averaged 586 mg. or 257 mg. per kilo. The adrenals of rabbits receiving thyroid for a corresponding interval of time averaged 282 mg.

per kilo. or 25 mg. per kilo. more than the mildly traumatized group.

6. The enlargement in all cases was largely if not entirely cortical.

7. The enlargement was not accompanied by definite histologic changes.

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THE EFFECT OF IODINE AND IODOTHYRINE ON THE LARVAE OF SALAMANDERS. I. THE EFFECT OF IODOTHYRINE AND IODINE ON THE METAMORPHOSIS OF AMBYSTOMA MACULATUM

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In 1918 I made some preliminary experiments on the effect of iodine upon the metamorphosis of salamander larvae; these were entirely unsuccessful and the intention of making further experiments on this problem was given up. Soon after this, however, Swingle (1) published his first experiments on the acceleration, by inorganic iodine, of the metamorphosis of tadpoles and the correctness of my own observations became doubtful. Therefore, I have repeated, following closely the method employed by Swingle, my former experiments on the larvae of salamanders. These experiments confirmed in every respect the observations made during my first experiments and revealed the astonishing fact that exactly the same treatment, i. e., the administration of inorganic iodine, which produces precocious metamorphosis in tadpoles, has not the slightest effect on the metamorphosis of salamander larvae, although iodothyrine causes prompt metamorphosis in the salamander larvae just as it does in tadpoles.

THE INFLUENCE OF IODOTHYRINE AND IODINE ON THE LARVAE OF AMBYSTOMA MACULATUM

In order to test the influence of inorganic iodine on the metamorphosis of the salamander larvae, two experiments, Experiments I and II, were carried out. The concentration of iodine used in these experiments was selected in accordance with the effect which iodine produced in similar experiments on the tadpoles of *Rana sylvatica*. With regard to the behavior of the salamander larvae kept in iodine solutions, as described below,

it may be pointed out that in these tadpole experiments a concentration of only 3 drops of a 1/20 M. solution per 1000 cc. of water was sufficient to cause a marked acceleration of limb development, while concentrations higher than 3 drops had a distinctly toxic effect on the tadpoles.

Experiment I. The eggs of one female of *A. maculatum* were freed from the common mass of jelly and placed into iodine-free water (10,000 cc. H_2O, 0.16 gm. Na_2CO_3, 0.04 gm. K_2CO_3, 0.4 gm. $MgSO_4+7H_2O$ and 0.6 gm. $CaCl_2$). This kind of water was used throughout the experiment. The temperature was room temperature (about 25°C. in average).

The larvae hatched on April 23, 1920, and on the same day were isolated into individual jars. The experiment consisted of 3 series, a control series LXXXIV (containing 5 larvae, one of which was preserved for histological examination 40 days after hatching), an iodine series LXXXVIII (containing 6 larvae), and an iodothyrine series LXXXIX (containing 6 larvae). Earthworms were used for food.

At an age of 14 days many larvae contracted an infection which resulted in a temporary retardation of growth (see Fig. 1), but did not interfere with the experiment, as it passed off soon. The growth as well as the course of the entire experiment are illustrated in Figure 1.

20 days after hatching: Nearly all larvae have developed 4 toes in the fore limbs and many have commenced to develop the first 2 toes in the hind limbs. At this stage the larvae of the iodine series are placed into water containing 3 drops of a 1/20 M. solution (in 95% alcohol) of iodine per 1000 cc. of water (equivalent to 0.6 mgm. iodine per 1000 cc. water), the larvae of the iodothyrine series into water containing 0.1 gm. iodothyrine (Bayer's powdered) per 1000 cc. of water (equivalent to only 0.03 mgm. iodine per 1000 cc. water).

33 days after hatching: At this date, 13 days after the first administration of iodothyrine, every single larvae of the iodothyrine series metamorphosed, although the size of the larvae was only 20 mm (see Table I).

34 days after hatching: Since the iodine has not the slightest effect on the metamorphosis of the larvae, the concentration is increased to 5 drops of iodine per 1000 cc. of water (equivalent to 1.0 mgm. iodine per 1000 cc. of water).

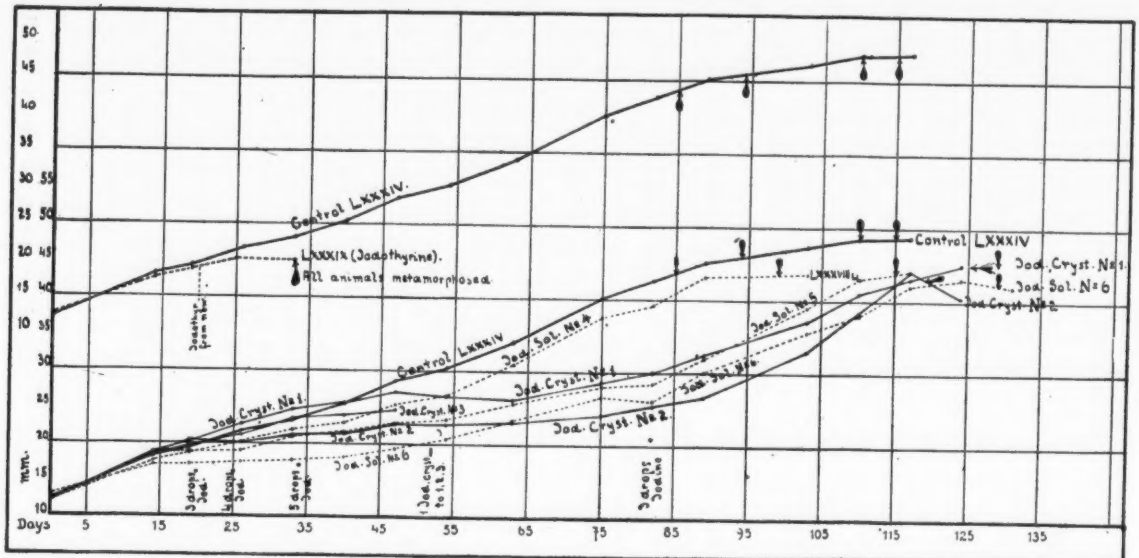

Figure 1. Experiment 1. The effect of iodine and iodothyrine on the metamorphosis of the larvae of *Ambystoma maculatum*. The thick black line in the upper and lower graph represents the growth of the control series LXXXIV (kept in iodine-free water), the dotted line of the upper graph represents the iodothyrine series LXXXIX, the three thin black lines and the three dotted lines of the lower graph represent each one individual of the iodine series LXXXVIII, the three black lines illustrating the growth of the three larvae that were kept in the iodine solution and at the same fed iodine crystals, the three dotted lines representing the growth of the three larvae which did not receive crystals, but were kept in the iodine solution. The amounts of iodine administered to the larvae are indicated on the bottom of the graph, metamorphosis of every individual larva is indicated by an arrow.

52 days after hatching: Since the iodine, except for a slight lowering of the rate of growth, had no effect as yet, it was suspected that the skin of the salamander larvae might be impermeable to iodine and that the small amounts of iodine swallowed with the water during feeding might not be sufficient to cause metamorphosis. Therefore, the larvae Nos. 1, 2 and 3 of the iodine series were fed each one crystal of iodine. This resulted in an immediate check of growth (see thin black lines in Fig. 1 at 54 days) and one larva (No. 3), which had received the largest crystal, was found dead the next morning.

Aside from this toxic effect no particular action of the iodine was noticeable; no acceleration of metamorphosis was caused. In fact, the larvae of the iodine series metamorphosed at a later date than the controls (see Table I and Figure 1; in Fig. 1 metamorphosis of each individual is indicated by an arrow).

In short, in the iodine series, metamorphosis, as is the case under normal conditions, was merely a function of growth; the larvae can not metamorphose before they have reached a certain size. That the size of the larvae of the iodine series was slightly

TABLE I

Experiment I. Duration of larval period and size of the larvae at the time of metamorphosis.

	Duration of larval period days	Size attained at the time of metamorphosis mm.
Control	101	48.7
Iodine (solution)	122	45.2
Iodine (solution-crystals)	124	43.3
Iodothyrine	33	20.0

smaller, at the time of metamorphosis, than the size of the controls, was due to the poor feeding of these larvae; starvation alone, without the administration of iodine, always results in a slight decrease of the size at which metamorphosis takes place, combined with an increased duration of the larval period. In the iodothyrine series, however, metamorphosis is distinctly independent of growth; the larvae are considerably smaller (more than 58 per cent) at the time of metamorphosis and at the same time the larval period is greatly abbreviated (by 67 per cent).

Experiment II. Quite similar was the result in another experiment. All larvae employed were from one female and were kept under the same conditions as those of Experiment I; in particular, iodine-free water was used in all series. In addition to earthworms, Enchytraeus and Tubifex were used as food. No infection occurred in this experiment.

The entire experiment consisted of 3 series, a control series LXXV (containing 6 larvae, one of which was killed for histological purposes before metamorphosis), an iodine series LXXIX (containing 6 larvae, 2 of which were killed for histological examination before metamorphosis), and an iodothyrine series LXXX (containing 6 larvae). The growth and metamorphosis as well as the entire course of the experiment are illustrated in Table II and Figure 2.

The iodine had no accelerating effect on metamorphosis, although in the beginning only a low concentration of iodine (2 to 3 drops of a 1/20 M. solution per 1000 cc. of water) was used so as not to interfere with growth. As this concentration, however, did not cause metamorphosis, the concentration of iodine was increased to 7 drops at an age of 60 days and to 8 drops of iodine per 1000 cc. of water at an age of 63 days. Yet even this high concentration of iodine did not result in precocious metamorphosis. Again 3 larvae (Nos. 1, 2, and 3, represented in Fig. 2 by the thin black lines of the lower graph), were fed iodine crystals, the feeding being repeated several times and even two crystals at the same time being fed once to Nos. 1 and 3. No. 3 died from this overdose, the other two larvae did not show precocious metamorphosis. No. 1 was killed for histological examination at an age of 82 days (3 of the control larvae had metamorphosed several days before this date); it showed no indication of metamorphosis. No. 2 metamorphosed later than any of the control larvae.

TABLE II

Experiment II. Duration of the larval period and size of the larvae at the time of metamorphosis.

	Duration of larval period days	Size attained at the time of metamorphosis mm.
Controls	80	52.2
Iodine (solution).....	79	49.6
Iodine (solution-crystals)..	89	40.9
Iodothyrine	58	29.8

The iodothyrine series of this experiment received a dose 10 times smaller than that used in Experiment I; only 0.01 gm. of iodothyrine was added to each 1000 cc. of water. Bayer's iodothyrine, the preparation used in these experiments, contains 0.3 mgm. iodine per 1 gm. of substance. Consequently, the iodothyrine larvae of this experiment received a dose of only 0.003 mgm. iodine per 1000 cc. water. Since the larvae of the iodine series were kept in a concentration of from 0.6 to 1.4 mgm. of iodine per 1000 cc. of water, the difference in the dose of iodine between the iodothyrine and iodine series was still greater in this experiment than in the previous experiment. Yet, as Figure 2 and Table II show, metamorphosis of the larvae of the iodothyrine series was again greatly accelerated and occurred precociously in regard to the size of the larvae as well as to the duration of the larval period. The size of the larvae, at the time of metamorphosis, was 43 per cent less than that of the controls, and the larval period was shortened by 28 per cent.

To summarize the results of Experiments I and II it seems evident that in salamanders metamorphosis cannot be accelerated by inorganic iodine, although iodothyrine (even if administered in doses containing much smaller amounts of iodine than those employed in the iodine experiments) promptly results in metamorphosis.

It may be mentioned that two experiments were carried out in which the embryos of *A. maculatum* were subjected to the influence of iodine and iodothyrine. In these experiments, too, iodine had no influence, while iodothyrine caused metamorphosis at a very early larval stage. Since these experiments will be described in detail elsewhere, I may confine myself to the above brief mention.

DISCUSSION

While in the larvae of the Salientia the administration of inorganic iodine causes precocious metamorphosis (2), the same procedure is incapable of accelerating the metamorphosis of the larvae of the tailed amphibians. That the ineffectiveness of inorganic iodine is not due to the employment of too low a concentration is shown by the fact that in both experiments the concentration of the iodine in solution was much higher than the concentration of iodine in an effective dose of iodothyrine, and the larvae fed crystals of inorganic iodine, in both experi-

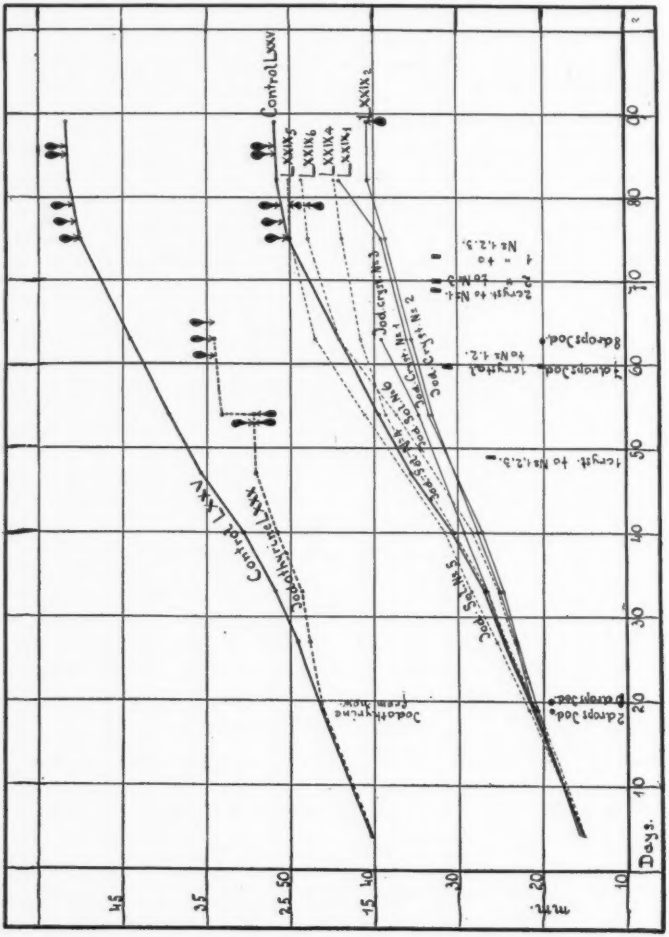

Figure 2. Experiment II. The effect of iodine and iodothyrine on the metamorphosis of the larvae of *Ambystoma maculatum*. The thick black line in the upper and lower graph represents the growth of the control series LXXV (kept in iodine-free water), the dotted line of the upper graph represents the iodothyrine series LXXX, the three thin black lines and the three dotted lines in the lower graph represent each one individual of the iodine series LXXXIX, the black lines illustrating the growth of the larvae (Nos. 1, 2, 3) which received iodine in the form of solution and crystals as well, the dotted lines representing the growth of the larvae (Nos 4, 5, 6) which received iodine in the form of solution only. The amounts of iodine administered to each larva are indicated on the bottom of the graph, metamorphosis of every individual is indicated by an arrow on the growth curve.

ments, received of course far more iodine than any of the larvae that were kept in iodothyrine.

The fact that inorganic iodine alone does not effect metamorphosis of the larvae of salamanders, while its administration to the closely related tadpoles results in metamorphosis, seems to elucidate further the nature of the thyroid mechanism.

On the basis of his work on the isolation and determination of the thyroid hormone, Kendall (3) has been led to conclude that iodine, although it is one of the constituents of the thyroid hormone, does not produce the "kind of reactivity" characteristic of thyroxin (the opening up of the indol ring when introduced into the body), but probably increases the "degree of this reactivity." In fact, the work of Kendall indicates, as pointed out by Kendall (4) that iodine is not split off as such from the molecule of the thyroid hormone during its action and that iodine per se is incapable of producing the effects typical of the thyroid hormone. Moreover, if the hydrogen on the imino in thyroxin is replaced by acetyl, without changing the position of the iodine atoms or decreasing the amount of iodine, thyroxin becomes completely ineffective. The physiologic tests on which Kendall's views are based were obtained in warm blooded animals.

When it became known, however, that the administration of inorganic iodine alone to tadpoles produces the same effects as does the administration of thyroxin, Kendall (5) changed his former theory and now assumes that thyroxin has two distinct and separate physiologic functions, i. e., "the effect upon the metabolic rate which is brought about by the CO-NH groups within the molecule, and the physiological changes involved in the metamorphosis of the tadpole brought about by the iodine contained in the molecule." In other words, Kendall now assigns to the iodine per se a particular function which it is able to exert also when detached from the molecule of the thyroid hormone.

Before the facts brought to light by the present experiments were known to me, I held (6) the view taken lately by Kendall; the behavior of the salamander larvae, however, shows that the assumption of an independent activity of iodine is not necessary and probably even not correct and that Kendall's first view covers more closely the facts. That the administration of in-

organic iodine, in some amphibian species, may result in precocious metamorphosis, does not prove by any means that iodine by itself causes metamorphosis. On the contrary, the experiments on salamanders show that inorganic iodine is quite unable to produce the structural changes involved in the amphibian metamorphosis. That administration of inorganic iodine, nevertheless, results in metamorphosis in the tadpole, while it is completely ineffective in the salamander larvae, is to be explained in the following way.

In previous work on the metamorphosis of salamanders I have been led to the conclusion that the thyroid gland of salamanders does not function during the largest part of the larval period. The excretion of a physiologically active hormone does not begin until shortly before metamorphosis; the latter phenomenon is the result of a large amount of hormone being suddenly thrown into the circulation. This is shown by various facts.

That at the time of metamorphosis the animals are suffering from severe hyperthyroidism is demonstrated by the growth curve (6). During larval life the growth is expressed by a steep and continuous line. At the time of metamorphosis, however, growth is suddenly checked and, for one or more weeks, considerable decrease in size takes place. A similar curve is produced, if metamorphosis, instead of by the animals' own thyroid glands, is caused by the administration of an excess of thyroid hormone. This suggests that at the time of metamorphosis normally a large amount of the hormone is suddenly excreted from the thyroid gland.

Second, the eyes of *Salamandra maculosa,* in order to undergo metamorphosis, need the action of the thyroid hormone; if, however, the hormone once has reached the eye, metamorphosis can be completed without the further action of the thyroid gland. During the largest part of the larval period metamorphosis of the eye can be prevented by removing the eyes to young larvae. Only if the larvae are very close to metamorphosis, removal of their eyes to young larvae does not any longer prevent metamorphosis of the grafted eyes. This fact indicates that not before a stage very close to metamorphosis is reached does the thyroid gland begin to discharge the thyroid hormone (7).

Third, removal of the thyroid gland does not interfere with

normal growth and development of salamander larvae as shown by Hoskins and Hoskins (8). This season I have extirpated the thyroid gland from several larvae of the species *Ambystoma maculatum* and so far have been able to confirm the observations made by the above named authors.

Although it seems certain, from these observations, that the thyroid gland of salamander larvae does not function during the largest part of the larval period, there may be found, in the larvae of salamanders, long before metamorphosis a thyroid gland completely mature as far as total size, histological structure of the cells of the follicular walls, size of the follicles and amount and staining capacity of the colloid are concerned. I have found this to be true for larvae of the species *Ambystoma opacum*, which externally did not show any indications of approaching metamorphosis and were preserved 7 weeks before the first larvae in the entire series metamorphosed. Similarly larvae which do not metamorphose at all, like the axolotl larvae of the species *Amybstoma tigrinum*, possess completely mature thyroid glands as shown by Allen (9). According to this investigator, axolotl larvae possess a thyroid fully as large as the thyroid glands of normal adults of the same size, the same size and number of follicles and the same amount of stainable colloid being present in both the axolotls and the normal metamorphosed adults.

It seems, therefore, that a mature condition of the thyroid and a large amount of colloid alone are not sufficient to permit of the normal function of the gland. One could, of course, imagine that the colloid of the larval thyroid, in spite of its chemical similarity with the thyroid of metamorphosing animals, as shown by the affinity for dyes, is not physiologically equivalent to the active thyroid hormone. This assumption, however, is probably not correct, since the investigations by Wilson and Kendall (10) as well as by Marine and his co-workers (11) have shown that the amount of active A-iodine containing principle present in a gland is directly proportional to the amount of normally staining colloid contained in the gland. It seems, therefore, that in the salamander larvae the thyroid gland is able to elaborate the normal active hormone, but is unable to excrete it.

In order to explain this condition I have assumed that hormone excretion in salamanders cannot take place before a certain

"releasing mechanism" (12) has developed, the action of which forces the thyroid to give up its hormone (14).

That the salamander metamorphosis is dependent on two factors, on the presence of a mature thyroid and of a peculiar releasing factor, is further suggested by the behavior of the salamander larvae when reared in low temperatures. It has been shown that the larvae of all species examined must become much larger, before they can metamorphose, when reared in low temperature, than larvae reared at higher temperatures (15). Since the development of the thyroid of the larvae kept at low temperature does not show a corresponding retardation, it seems that at low temperatures the development of a second factor necessary for metamorphosis is more retarded than growth and the development of the thyroid gland.

It is obvious from these facts that the administration of inorganic iodine could be expected to influence metamorphosis of the salamander larvae only, if inorganic iodine as such could bring about changes in the amphibian organism similar to those caused by the thyroid hormone or if the salamander larvae would possess, besides the thyroid gland, other tissues which can take up the iodine, elaborate from it the thyroid hormone and excrete it without the intermediation of a particular releasing mechanism. Since, however, the present experiments definitely show that the administration of inorganic iodine does not cause precocious metamorphosis, it is obvious that inorganic iodine as such is unable to produce the structural changes involved in the amphibian metamorphosis and that, in salamanders, the thyroid is the only tissue which can elaborate, from the iodine, the thyroid hormone.

The salamander larvae are in this respect fully comparable to the mammalian organism. As shown by the athyroidous cretin iodine does not produce any effect similar to that caused by the thyroid hormone. Administration of inorganic iodine causes an effect similar to the action of thyroid hormone only in the case of a leakage of the thyroid gland, such as is found in persons suffering from exophthalmic goiter; in patients suffering from exophthalmic goiter the symptoms of hyperthyroidism are aggravated after iodine administration, because the presence of an excess of iodine leads to the elaboration and, due to the leakage of the thyroid gland, to the excretion of still larger amounts of the thyroid hormone.

And in a leakage of the thyroid apparatus, it seems to me, we must seek the explanation of the peculiar reaction of the tadpole towards the administration of inorganic iodine. For it has not been shown that in the tadpole or in any other vertebrate the inorganic iodine need not combine first with the other substances which constitute the active principle of the thyroid hormone. The present experiments show that inorganic iodine as such is unable to cause the amphibian metamorphosis. It is, therefore, much more probable that the tadpole can react on iodine administration with metamorphosis, not because of a direct action of the inorganic iodine as such, but on account of a peculiar thyroid mechanism of the tadpole. It is probable that in the tadpole organism the thyroid function has not attained a complete centralization as it has in higher vertebrates, but besides the thyroid other tissues have the ability of manufacturing the thyroid hormone. While the thyroid gland of most organisms that are in the possession of a thyroid apparatus is able to store the thyroid hormone, these tissues are unable to store the hormone after its elaboration. As Swingle (16) points out, this lack of the storage ability is the reason why an excess of iodine must be supplied to the tadpoles after thyroidectomy, in order to produce metamorphosis. It is a well known fact that, in contradistinction to the salamander larvae, the tadpoles show the effects of thyroid action very early in larval life, as indicated by the course of limb development in this group of amphibians; very probably this is due to a constant though slight "leakage" of the tadpole thyroid apparatus.

The existence of a particular releasing mechanism, as I have assumed it in salamanders, has recently been much emphasized for the thyroid of warm-blooded animals through the investigations of Cannon and Fitz (17) and of Wilson and Durante (18) and is assumed to be in this case of nervous nature. That the administration of inorganic iodine in the normal mammalian organism has no effect comparable to that of the thyroid hormone, although an excess of hormone is manufactured under these conditions [Marine and Rogoff (19)], may have its cause, too, in the action of such a releasing mechanism which under normal conditions permits only a definite amount of the hormone to escape from the thyroid gland.

In conclusion it may be said that according to these views it is impossible to test the effect of inorganic iodine as such in tadpoles, larvae of salamanders and normal warm-blooded animals. The only animal which can give an idea of this effect is the athyroidous warm-blooded vertebrate, as such an organism positively does not possess the ability of storing the iodine or combine it into the thyroid hormone. The experiments which have been undertaken on such individuals (congenitally athyroidous persons and thyroidectomized mammalians) have shown, however, that inorganic iodine, if not bound to the thyroid hormone, has no effect comparable to that of the thyroid hormone. It is especially this failure of inorganic iodine to change conditions in the cretinous person, which forms the basis of Kendall's theory that iodine plays an unimportant role in the reactivity of the thyroid hormone.

The views elaborated above are in no way contradictory to the fact that nevertheless, in a biological sense, iodine is an important and essential part of the thyroid hormone; if it were possible to substitute the iodine by any other substance without changing the reactivity of the thyroid hormone, biologically this would not make iodine less important; for it is the only substance which, by the mechanism actually available to the organism, can be used in the manufacture of the thyroid hormone. Although chemically bromine or any other halogene may be able to substitute iodine without changing the chemical or even the physiological reactivity of the thyroid hormone, the organism is unable to use bromine, as shown by Swingle (20), and presumably the other halogenes to make thyroid hormone.

That iodine if supplied in excess does not produce metamorphosis of salamander larvae, does not mean, according to what has been said above, that it is not necessary in the metamorphosis of salamanders. Very likely if the larvae of salamanders would be raised on an iodine-free diet and kept in iodine-free water, metamorphosis could not take place. Nevertheless it may turn out that the salamander larvae need far smaller amounts of iodine for metamorphosis than the tadpoles do. There are certain species of salamanders (*Aneides iecanus* and *Aneides lugubris*) which can complete metamorphosis without leaving the egg envelops. The larvae of these species have no opportunity to procure iodine from the outside environment,

the iodine contained in the eggs being apparently sufficient for metamorphosis. But the eggs of amphibians have never been examined as to their iodine content; it is possible that the eggs of salamanders contain more iodine than those of the tailless batrachians and that the eggs of the two species referred to above contain even more iodine than the eggs of the other salamanders.

SUMMARY

1. Administration of inorganic iodine to the larvae of the Salamander *Ambystoma maculatum* does not cause precocious metamorphosis.

2. Inorganic iodine as such is unable to produce the structural changes involved in the amphibian metamorphosis.

3. In salamanders the thyroid hormone is not excreted during the largest part of the larval period, while in tadpoles excretion of the thyroid hormone begins early in larval life.

4. This explains why the administration of an excess of inorganic iodine can produce precocious metamorphosis in tadpoles while it is completely ineffective in the larvae of salamanders.

5. In order to cause metamorphosis, iodine must combine with the substances forming the nucleus of the thyroid hormone and the rate of hormone excretion must increase with the increase of iodine available.

6. In salamanders the rate of hormone excretion is not influenced by an excess of iodine, but depends on the action of a particular "releasing mechanism."

7. There is at present no fact known, which would prove, that inorganic iodine as such can function as a hormone.

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12. Although the existence of such a "releasing mechanism" is well suggested by its physiological action, there are at present no facts known which would throw light on the nature of this mechanism. Since the expression "excretor substance" used in former papers (13) has caused unjustified speculation on the part of other investigators and even lead to the fully unwarranted claim on the part of one writer that the excretor substance is a protein, I have preferred to replace the term "excretor substance" by the completely indifferent and merely auxiliary term "releasing mechanism," which serves to designate the physiological function, but does not anticipate anything concerning the nature of this factor.

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Book Reviews

A Primer for Diabetic Patients. By Russell M. Wilder, Ph.D., M.D., Mary A. Foley, Dietitian, and Daisy Ellithorpe, Dietitian, Phila. & Lond., 1921. W. B. Saunders Co., 76 p.

For review see Am. J. Med. Sc., 1921, **162,** 127.

Diabetes and Its Diatetic Treatment. Ninth edition. By B. D. Basu, Bâhadurjanj, Allahabad, 1918. Panini Office, 104 p.

For review see Presse Méd., **27,** 738. Conditions among the Hindus are especially considered.

Diabetes Mellitus. A System of Diets [etc.]. By Herman O. Mosenthal, M.D., New York, 1921. Paul B. Hoeber.

For review see J. Am. Med. Ass., 1921, **77,** 1360.

Le Diabete Sucre. Marcel Labbé, Paris, 1920. Masson et Cie, 375 p.

Reviewed in Physiol. Abst., 1921, **5,** 510-511.

Die Lymphocytose. Dr. S. Bergel, Berlin, 1921. Julius Springer, 140 p.

Though this highly interesting book is not primarily on an endocrine topic, it bears upon various endocrine problems and may, therefore, shortly be mentioned here. The function of the polynuclear cells is to deal with foreign proteins, toxins or micro-organisms. The function of the lymphocytes is, as Bergel has shown by most beautiful experiments, the defense against foreign lipoids. Thus, tuberculous pus consists chiefly of lymphocytes because the tubercle bacillus contains a large amount of lipoids. It is the same with the spirochaeta pallida and with the leprabacillus. As lipoids play an enormous part in the organism the role of the lymphocytes, which prepare a lipase, is equally important. In disturbances of the fat metabolism this is frequently observed and so a relation between status thymo-lymphaticus (the *thymus* and the lymph glands being the origin of the lymphocytes) and *adiposity* becomes comprehensible in this way. Because the thymus has probably a more intense function in young children, these children have more lymphocytes in their blood than older individuals.

The cortex of the *adrenals* has, perhaps, a certain relationship to lipoid metabolism and it is remarkable that histologically it contains large numbers of lymphocytes, which have a great affinity for lipoids. Diseases of the *thyroid,* which give rise to disturbances in fat-metabolism (Graves' disease) often are accompanied by lymphocytosis. Injection of thyroidin produces loss of fat and lymphocytosis.

Also in *diabetes,* where not only a disturbed fat metabolism may exist, but where often much fat is given with the diet, lymphocytosis is not rare. It is remarkable that lymphocytes which contain cholesterin form the *xanthoma diabetica.*

These few remarks may indicate the importance of this book not only for the biologist and pathologist, but also for those especially interested in endocrinology.—J. K.

NUOVE IDEE SUL DIABETE ZUCCHERINO (NEW IDEAS ON DIABETES), by Prof. Giuseppe Vigevani, Milan, 1920. Remo Sandron, 191 p.

Professor Vigevani tries to describe in this book the newer theories on diabetes mellitus and he has been able to do this in a very readable way. But it is another question whether the book must be considered as highly scientific literature. The abstractor hardly dares to give his opinion on this point, for the book is a mixture of original, interesting remarks and as many unproved statements. The author does not consider the pancreas as the only cause of diabetes. This seems, according to our present knowledge, perfectly true. His statement that no monoglandular diseases exist will not be denied by many investigators. His remark that in treatment of diabetes it is not enough to treat the glycosuria is certainly right; he states that in some cases, e. g., in cases with Graves' disease or in cases of a specific nervous character, it may even be harmful to restrict carbohydrates and that it is much better not to give animal protein. On the other hand, he considers the hypophysis as the most important organ for the regulation of growth, metabolism and sexual functions. He firmly believes that the hypophysis has an enormous importance in diabetes; the investigations of Camus and Roussy on this point are shortly and incompletely mentioned and no further notice is taken of them; the work of Leschke, who probably proved that the hypophyseal diabetes is of cerebral origin, has been overlooked. Vigevani describes even some cases which apparently have been cured (?) by administration of extracts of hypophysis.

It is amusing that in this book of new ideas nothing is said of the newer dietetic treatment, though many pages are devoted to organotherapy. The newer American and English literature on the subject has been almost entirely omitted.—J. K.

Abstract Department

Metabolism in ADIPOSITY (Zum Fettstoffwechsel bei der Fettsucht). Rolly (F.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 887-889; 917-919.

Rolly compared the metabolism in two patients who first had been thin and later became fat. The metabolism of a patient with tuberculosis was carefully examined. I. The height was 1.67 M. and weight, 56.7 K. Double castration had been done for tuberculosis of the testicles. Two and a half years after the first metabolic study he weighed 86.1 K. At this time his metabolism was again studied. When a large quantity of food was ingested the oxydations, as was proved by a study of the gaseous metabolism, were much less increased than before the operation. II. A woman with Graves' disease was treated by partial **thyroidectomy.** After a childbirth she became fat. While she was suffering from Graves' disease the oxydation capacity was high. After strumectomy the same change was observed as in the first patient. After childbirth she took on more weight while the oxydation capacity sank more and more. When meat was administered at the time she was thin, a marked rise in oxydation was seen. When she was stout this rise was much less marked and much slower. The administration of thyroid produced a rise in oxydation.—J. K.

Estimation of ADRENALIN in the adrenal (Bestimmung der Adrenalins in der Nebenniere). Autenrieth (W.) & Quantmeyer (H.), München. med. Wchnschr., 1921, **68**, 1007-1008.

Description of a colorimetric method. The adrenal is ground with sand and N/10HCl, heated to boiling and then 10% sodium acetate is added, after which it is boiled again. A solution of phosphotungstic acid and then sodium carbonate are added to the filtrate. The blue color which develops is compared with that developed from a known solution of adrenalin.—J. K.

(ADRENAL) Maligner Sympathicustumor. Barnewitz. Berl. kiln. Wchnschr. 1921, **58**, 979.

Abstracted from same article published elsewhere.—J. K.

Radiation of ADRENALS in DIABETES (Röntgenbestrahlung der Nebennieren bei Diabetes). Beumer, Berl. klin. Wchnschr., 1921, **58**, 855.

In a boy of 6½ years with severe diabetes the adrenals were submitted to x-ray treatment. The blood sugar immediately

became normal but the glucosuria and the carbohydrate tolerance did not improve. Diacetic acid and creatin disappeared from the urine, while the quantity of excreted ammonia was diminished.

—J. K.

(ADRENALS) Formation of pigment in Addison's disease (Die Pigmentbildung beim Morbus Addisonii). Bittorf (A.), Deutsches Arch. f. klin. Med. (Leipzig), 1921, **136**, 314-322.

The pigment in Addison's disease is formed in the epithelium. In this epithelium of the skin an oxidizing enzyme (oxydase) is found capable of changing certain aromatic substances into melanins. Bittorf believes it to be a tyrosinase. Bloch believes it to be a special tyrosinase; a so-called dopa-oxydase, an enzyme, changing 3-4 dioxyphenylalanin into melanin. This enzyme is found only in young epithelial cells. To explain the increased formation of pigment in Addison's disease, there are three possibilities: (1) More oxydase is formed; (2) those substances are formed which are oxidized into pigment; (3) a combination of 1 and 2. The author examined these theories in one case. He first found that a piece of skin from a case of Addison's disease when kept in the incubator at 37° rapidly becomes darker. In this case, however, this was not very marked and therefore he concludes that not always is there an increase in the substance the oxydation of which produces pigment. When a piece of skin from the same source is kept in a solution of adrenalin it darkens more rapidly than in other solutions. Normal skin, even when darkly pigmentated, does not become darker in a solution of adrenalin. Microscopically it is found that the epithelial cells carry the pigment. Most of it is found in the corium. Therefore it is concluded that the pigmentation is due to an increased oxydation of adrenalin in the skin. An increased quantity of oxydase is therefore probable.—J. K.

Unilateral ADRENAL ablation in man (Einseitige Nebennierenexstirpation beim Menschen). Boenheim (F.), Berl. klin. Wchnschr., 1921, **58**, 1133.

Hyperacidity of the stomach contents is often found in epilepsy. After the removal of one adrenal this hyperacidity disappears. Sodium chloride is often retained in the body in epilepsy. After the removal of an adrenal the elimination of chloride is normal. It is remarkable that in epilepsy the amount of sodium chloride in the blood is low and that after the operation it becomes normal. This low content of sodium chloride in the blood as well as urine proves that it must be retained in the tissues. The carbohydrate metabolism, which is normal in epilepsy, does not undergo any change following unilateral adrenal ablation.—J. K.

ADRENALIN hyperglycemia (Ueber die Adrenalinhyperglykaemie). Brösamlen, München. med. Wchnschr., 1921, **68**, 964.

Adrenalin when injected into healthy persons produces an average increase in blood sugar of ±0.058%; in most cases this rise in blood sugar does not cause glycosuria. When there is glycosuria it generally starts 3 hours after the injection and is finished within a few hours (maximum 11 hours). The hyperglycemia is observed approximately 10 minutes after the injection and reaches its maximum in about one hour. Two to three hours after the injection there is a slight hypoglycemia which is followed by a normal amount of blood sugar. The maximum increase in blood sugar is generally seen at a moment when the influence on pulse or blood pressure has already passed away. In **Graves' disease** the reaction of hyperglycemia is stronger than in normal persons. In **thyrotoxicosis** no constant changes are found; also in **diabetes** the reaction of hyperglycemia shows no constant features. Perhaps the study of this reaction may enable us to distinguish different types of diabetes.—J. K.

(ADRENIN) Roentgen-ray studies of bronchial function. Bullowa (J. E.) & Gottliel (C.) Am. J. M. Sc. (Phila.), 1920, **160**, 98-106.

This study is an attempt to determine the processes by which the lungs evacuate themselves. After unsuccessful experiments with thorium in sodium citrate solution, barium in acacia and barium in gelatin, barium sulphate was triturated with anhydrous olive oil until a thick, smooth paste was formed. This paste was injected into the bronchus of an anesthetized dog. A bellows-like action in the trachea and bronchi, which may be limited by contraction of the bronchial muscles, was observed. A peristaltic action of the bronchial muscles, which seemed adequate to empty the bronchi without invoking ciliary movements also occurred. The authors in certain of these experiments injected adrenalin into dogs after filling their bronchi with barium. To their surprise, the bronchi became smaller. This same effect was observed when the injection of the adrenalin occurred before the barium. In one dog benzolbenzoate was given; this caused bronchial dilatation. Adrenalin was given and the bronchi were found contracted. In another dog bronchial spasm was induced by administering 1 mg. of muscarin. An intravenous dose of adrenalin relaxed the spasm.—J. F.

The function of the ADRENALS (De rol der bijnieren). de Caestecker, Vlaamsche Geneesk. Tijdschr. (Ghent.), 1921, **2**, 392-399.

A general review without new data.—J. K.

Medullary malignancies of the SUPRARENAL gland with a report of cases. Carter (W. H.), Am. J. Dis. Child. (Chicago), 1921, **22**, 244.

Tumors of the suprarenal cortex produce a symptomatology quite different from those of the medulla. Cortical neoplasms give rise to premature sexual development described by Bullock and Sequeira and the type in which the features are precocious obesity and muscular hypertrophy (Guthrie and Emery). Malignant neoplasms of the medulla occur only during childhood, and are of two types: the Pepper type with liver metastases and the Hutchinson type with secondary growth in the bones of the skull, sternum, vertebrae and the long bones.

Carter concludes that malignant medullary neoplasms are not unusual. In the majority of cases orbital hemorrhage is the first sign observed. Diagnosis is not difficult once the orbital hemorrhage has occurred. The disease is likely to be mistaken for trauma, chloroma or scurvy. Surgical interference can only palliate since metastases usually occur before a diagnosis can be made. Metastases probably occur in the lymph stream. The tumor rarely may metastasize to the skin. The suprarenal medulla being of neuro-ectodermic origin, the tumors resemble malignant neoplasms of the sympathetic nervous system and they are correctly designated as neuroblastoma. The article includes a report of three cases, the details of which are not of immediate endocrine interest.—M. B. G.

The sensitiveness of the human organism to ADRENALIN (Zur Frage der Adrenalinempfindlichteit des menschlicken Organisms). Csépai (K.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 953-954.

When 1 mgm. of adrenalin is injected subcutaneously the blood pressure rises. The way in which this develops—the rapidity and the intensity—have been considered by some authors as a method for diagnosis of the irritability of the involuntary nervous system. Csépai, however, points out that the effect of a subcutaneous injection is not in the first place due to the rapidity of absorption. He therefore injected very small quantities (0.01-0.04 mgm.) adrenalin intravenously. He often observed cases in which there was no increase in blood pressure after subcutaneous or intramuscular injection of adrenalin but in which there was a normal rise after intravenous injection. Only in dying persons no reaction is seen. The difference seen after subcutaneous injections in different persons is a simple difference in absorption and has no relation whatever to the irritability of the voluntary nervous system.—J. K.

ADRENAL and antigens (Nebenniere und Antigene). Emmerich, Berl. klin. Wchnschr., 1921, **58**, 556; Deutsche med. Wchnschr. (Berl.), 1921, **47**, 666.

Human adrenals may be valuable as antigens in the Wassermann test when they contain enough lipoids. The best antigen is made from adrenals from patients with arteriosclerosis; in cases of

tumors, scarlet fever or acute yellow atrophy of the liver the adrenals are not always fit for preparing antigens. The adrenals of horses are valuable for preparing antigens for the Wassermann test and the flocculation test of Sachs and Georgi.—J. K.

(ADRENAL) Ether hyperglycemia and glycosuria on the rabbit. Fujii (I.), Tohoku. J. Exper. M. (Sendai), 1921, **2**, 169-208.

The author, using rabbits as subjects, investigated the effect on ether glycosuria and ether glycemia of (1) depth of anesthesia; (2) changes in body temperature; (3) bilateral splanchnectomy, and (4) variation in adrenal secretion. The latter was determined by the difference in degree of staining of the two adrenals after ether anesthesia preceded by a unilateral splanchnectomy. He noted that the degree of ether hyperglycemia and glycosuria was roughly proportioned to the depth of anesthesia. Ether hyperglycemia occurred in animals whose body temperature was maintained at normal. If the temperature were allowed to fall the hyperglycemia increased. Bilateral splanchnectomized animals developed some hyperglycemia from ether anesthesia. Rabbits with unilateral splanchnectomy developed the same degree of ether hyperglycemia as normal animals. The chromaphil substance in the adrenal on the side of the cut splanchnic always stained more deeply than the other.—E. L. R.

Treatment of paralysis of the heart in narcosis with intracardial injections of ADRENALIN (Bekämpfung des Narkose-Herzstillstandes durch intrakardiale Adrenalininjektion). Frenzel (H.), München. med. Wchnschr., 1921, **68**, 730-732.

In many cases the injection of 0.1 cc. of a 1% solution of adrenalin into the heart gave good results.—J. K.

(ADRENIN) Comparative examination of arterial, capillary and venous blood in man (Vergleichende Untersuchungen am arteriellen, kapillaren and venösen Blut des Menschen). Hesz (O.), Deutsches Arch. f. klin. Med. (Leipzig), 1921, **137**, 200-224.

Comparative examination of the blood in arteries, veins and capillaries of the forearm has shown that normally the venous and capillary bloods contain the same quantity of erythrocytes, while the arterial blood often contains a greater number. Heart lesions seem to result in an increased number of erythrocytes in the capillaries. Artificial venous stasis is followed by an increase of erythrocytes in veins and capillaries and a decrease in the arteries. Hesz has endeavored to find out whether the rise in blood pressure following injection of adrenalin causes a change in blood concentration. He finds that the number of corpuscles in arteries and veins is increased; in the capillaries, however, it is diminished. Often

the maximum number of corpuscles and the maximum blood pressure are not synchronous. Therefore it is concluded that the changes in concentration are not due to the changes in blood pressure.—J. K.

(ADRENIN: THYROID) The Goetsch test (L'epreuve de Goetsch). Garnier (M.), & Bloch (S.). Bull. et mém. Soc. méd. d. Hôp de Par., 1921, **45**, 1137-1142.

A report of the application of the Goetsch test to 48 patients. Out of the group 16 gave a definitely positive reaction, 10 gave a weakly positive reaction and 22 were negative. Among the cases which failed to react were 3 with Basedow's disease, and 2 with myxedema. In cases of transitory hyperthyroidism the reaction is not given after the disturbance has subsided.—F. S. H.

Intracardial injection of ADRENALIN and strophanthin in acute cardiac paralysis (Intrakardiale Einspritzung von Adrenalin-Strophantin bei akuten Herzlähmungen). Guthmann (H.), München. med. Wchnschr., 1921, **68**, 729-730.

The author recommends the injection of 1 mgm. adrenalin and 1 mgm. strophanthin into the heart in acute cardiac paralysis. In all cases in his experience the heart began to beat again. In 3 patients that died no changes were seen in the heart at autopsy. —J. K.

Suggestions for the Austrian Pharmacopeia. IX. Adrenalin. Heisler (R.), Pharm. Post., 1918, **51**, 677-678; Chem. Zentralbl., 1919, **2**, 208-209.

H. demands an absolutely colorless adrenalin solution. Brown, red or cloudy solutions are to be rejected, while faintly rose-colored are permissible. The acidity limit should be fixed at 0.25 cc. 0.1 N NaOH per 5 cc. of 1% adrenalin solution, methyl orange being used as indicator.—Chem. Abst., **13**, 2730.

The influence of ADRENALIN on the blood picture (Zur Beeinflussung des Blutbildes durch Adrenalin). Hoefer (G. A.) & Herzfeld (E.), Folia haematologica (Leipzig), 1921, **27**, 77-95.

In normal subjects injection of adrenalin is generally followed by changes in the numbers of leucocytes. First there is a marked lymphocytosis with a more or less intense increase in neutrophil cells. Then the number of lymphocytes sinks, often below normal, with a slight increase in polynuclear cells. In rare cases a third phase with marked leucocytosis and slight lymphocytosis is observed. In a case of pernicious anemia without pathological cells in the blood (the only morphological symptoms in the blood being aniso- and poikilo-cytosis), normoblasts and basophil punctuated cells came into the circulation after injection of adrenalin. In the

same way in a case of "pseudobanti" myelocytes, which had not been found before, appeared in the circulation. In a case of acute myeloid leucemia first the polynuclear cells showed an enormous increase. Then their number went down, to rise after this for a second time. The small number of leucocytes and the myelocytes also showed an increase.—J. K.

The white ADRENAL line (Sergent); its clinical significance. Kay (W. E.) & Brock (S.), Am. J. M. Sc. (Phila.), 1921, **191**, 555-561.

From a study of a series of 255 cases of a variety of diseases and normals upon which numerous pharmacologic and other tests were performed, the authors conclude that the so-called white adrenalin line of Sergent is a local vasomotor reflex, resident in the skin, bearing no direct relationship to adrenal gland activity. They give as their reasons: its independence of blood-pressure, acute fatigue, and other signs of hypoadrenia; its frequent occurrence in normals and in a variety of diseases unassociated with hypoadrenia; its reappearance in the face of persistent general manifestations of adrenalin subcutaneously administered; its peculiar association with scarlet fever. It would appear that the state of the vasomotor system which allows of its best exhibition is found in young adults of either sex, and especially in the exanthem of scarlet fever. On the basis of this series it is stated that this line has not the clinical significance attributed to it.—J. F.

Tuberculous ADRENAL in Addison's disease (Tuberkulöse Nebenniere bei Morbus Addisonii). Kraus (E. T.), Berlin klin. Wchnschr., 1921, **58**, 1086.

In a case of Addison's disease with tuberculosis of an adrenal the pancreas was much atrophied. This supports the theory of Falta, that there exists an antagonism of pancreas and adrenal.—J. K.

Tuberculosis of ADRENAL (Tuberculose einer Nebenniere). Kraus (E. T.), Wiener klin. Wchnschr., 1921, **34**, 518.

In a case of Addison's disease a tuberculous adrenal was found, with a marked atrophy of the pancreas.—J. K.

ADRENALS and Epilepsy. Kutschera (L.), Deutsche med. Wchnschr., Berlin, 1921, **47**, 1282.

In two cases of epilepsy the author removed the left adrenal. The effect was only temporary.—J. K.

(ADRENIN) Urticaria, classification of types and its causes. Lambright (G. L.), Am. J. M. Sc. (Phila.), 1921, **162**, 183-187.

In this paper, the author incidentally reports a case of urticaria following injection of foreign protein (antidiphtheritic serum) which

adrenalin relieved entirely, but it soon reappeared and lasted for several days.—J. F.

(ADRENAL) Pathology and histology of Addison's disease (Zur pathologichen Anatomie und Histologie der Addisonschen Krankheit). Lubarsch, Berlin klin. Wchnschr., 1921, **58,** 1195.

A short note. Addison's disease is often complicated by **status thymolymphaticus.** In this case there was no tuberculosis, but a very marked status thymolymphaticus even including the **thyroid.**

El tratamiento del asma bronquial por la ADRENALINA en inyecciones hipodérmicas e intramuaculares. Rev. med-quir. (Tegucigalpa, Honduras), Maira (O.), 1919-20, **1;** No. 4, 6-14; Anales Fac. d. med. de Montevideo, 1919, **4,** 515-531.

Maira reiterates that many years of experience have convinced him that epinephrin is the treatment par excellence for combating attacks of asthma. These patients stand large doses. One had suffered from asthma for fifteen years when subcutaneous injections of epinephrin were begun in 1914, with prompt relief for several hours. The dose was 15 drops, and it was repeated twice and sometimes three or four times a day. This has been kept up for five years, with more than 300 injections, and no by-effects have been observed. Maira has seen nothing to indicate that epinephrin brings on arteriosclerosis when given by subcutaneous or intramuscular injection. The latter is preferable when rapid action is desired. He has obtained good results with it also in whooping cough.—J. Am. M. Ass.

(ADRENIN) Blood volume and blood volume methods. Lamson (P. D.) & Nagayama (T.), J. Pharmacol. & Exper. Therap. (Balt.), 1920, **15,** 331-346.

After injection of adrenin (0.9 mgm. per kilo) there is an increase in red cell concentration and a decrease in plasma volume, an actual loss of fluid into liver lymphatics, for if the liver is previously removed there is no change in red cell concentration. —F. A. H.

The influence of ADRENALIN on the voluntary muscles (Die Wirkung des Adrenalins auf die Skelettmuskulatur). Lange, Wien. klin. Wchnschr., 1921, **34,** 386.

Adrenalin diminishes the permeability of the sarcolemma and alters the irritability of the voluntary muscles. (No details are given.)—J. K.

Influence of glands with internal secretion on the respiratory exchange. II. Effect of SUPRARENAL insufficiency (by removal or by freezing) in rabbits. Marine (D.) & Baumann (E. J.), Am. J. Physiol. (Balt.), 1921, **57,** 135-152.

Rabbits display a wide variation in the duration of life following double suprarenal ablation, and it is thus possible to get a graded series for metabolic studies. Observations were made at 2 hour intervals, after control metabolic rates had been established for several weeks. Respiratory exchange was determined by the modified Haldane apparatus. The conclusion is that removing or crippling (by freezing) the suprarenals results in a metabolic disturbance, characterized by increased heat production and CO_2 output, definitely related to the completeness of removal of the cortical function. The symptom complex somewhat resembles that of exophthalmic goiter.
—T. C. B.

L'ADRÉNALINE dans le choléra. Naamé, Gaz. de Hôp, civ. et mil. (Paris), 1921, **94**, 678-679.

The author cites evidence that has convinced him that the symptomatology of cholera is to be ascribed to adrenal deficiency. The deduction is based on the allegations that the suprarenal glands in cholera show characteristic degenerative lesions and that adrenin has remarkable curative effect in this disease.—R. G. H.

The calcium ion as an antagonist of ADRENIN (Het calcium ion als antagonist van adrenaline bij vaat doorstrooming en bloedsdruk). Noyons (A. K.), Nederl. Tijdschr. v. Geneesk. (Haarlem), 1921, **65 (II)**, 793-794.

The experiments were carried out on rabbits with a cannula in the abdominal aorta and a cannula in the inferior vena cava. When calcium is added to the solution the vasoconstricting effect of adrenin is decreased. When, however, a calcium salt is added and at the same time sodium acetate, no influence of this mixture is seen on the activity of adrenin. When an animal repeatedly gets injections of calcium chloride, until the amount of calcium in the blood is larger than normal, adrenin does not produce a rise of blood pressure. When, however, in such an animal citrate of sodium is injected, adrenin again has its ordinary effect on the blood pressure. Either calcium or adrenin alone has a vasoconstricting action. Together, however, they neutralize each other.—J. K.

(ADRENIN) Vascular reactions in vascular hypertension. O'Hare (J. P.), Am. J. M. Sc. (Phila.), 1921, **159**, 369-380.

This is a study of the effects of rest, excitement, nitroglycerine, and adrenalin upon patients with high-blood pressure and normal renal function. The observations were carefully made. Adrenalin, 0.5 cc. of 1:1000 solution, was given intramuscularly after the normal base line for the blood pressure had been determined. Frequently readings were taken then until the pressure returned to this base line. It was shown that in this type of case the vessels were especially sensitive to adrenalin, a marked rise in pressure—often an

alarming one—taking place immediately after its injection, intramuscularly.—J. F.

EPINEPHRIN hypersensitiveness and its relationship to hyperthyroidism. Peabody (F. W.), Sturgis (C. C.), Tompkins (E. M.) & Wearn (J. T.), Am. J. M. Sc. (Phila.), 1921, **161**, 508-517.

From the application of the Goetsch test to a series of patients, these workers conclude that different individuals, both sick and well, react with different degrees of intensity to the injection of epinephrin and that the fundamental nature of the reaction is unknown. But it seems probable that it is due to a stimulation of the sympathetic nervous system. Therefore, there would be no reason for assuming that a positive reaction is constantly associated with hyperthyroidism. The "positive" reaction is frequently associated with this disease, but not always. It is also found in many psychoneurotics, in about 50 per cent of patients convalescent from acute infection, in about the same proportion of soldiers with "effort syndrome," and in 14 per cent of apparently healthy young medical students.—J. F.

ADRENAL tuberculosis and biliary lithiasis (Tuberculosis suprarenal y litiasis biliar). Raverot (M.) & Bacigalupo (J.), Semana Méd. (Buenos Aires), 1921, **28**, — — (No. 17).

Post-morten examination in a young girl showed tubercular destructions of the adrenal capsules. A calculus was found in the gall duct.—B. A. H.

ADRENALIN and anti-pneumococcic serum injection in primary pneumopathies for provocation of the crisis (Provocation de la crise salutaire dans les pneumopathies primitives par l' injection intraveineuse de sérum antipneumococcique et d' adrénaline. Statistique, résultats. Interpretation). Renaud (M.), Bull. et mém. Soc. méd. d. hôp. de Par., 1921, **45**, 919-927.

Renaud reports a mass of data from some 750 cases of pneumonia in many of which he provoked the crisis by the intravenous injection of 0.5 mgm. of adrenaline in combination with anti-pneumococcic serum. He considers his results justify the use of the drug in such cases.—F. S. H.

The preparation and preservation of ADRENALIN solutions. Richard (F.) & Malmy (M.), J. pharm. chim. (Paris), 1921 (7), **23**, 209-214.

The adoption of an official solution of adrenalin (1:1000) is urged because of the great variations in the formulas of the solutions sold at present. Tests show that solutions made by the aid of SO_2, with physiological salt solution as base, are best; the SO_2 acts as solvent, antiseptic and preservative. The adrenalin is dissolved in

100 cc. of physiological salt solution (7.5 gm. NaCl per l.) containing 10 gm. SO_2 per l. (controlled by back titration with 0.1/N I_2), and brought to 1000 cc. by the addition of sterilized physiological salt solution. This solution must be made in the absence of NH_3 fumes. If preserved in ampoules, filled in an atmosphere of CO_2 it has been kept a year.—Chem. Abst., **15**, 2335.

(ADRENAL) A case of Addison's disease treated with success by tuberculin (Enfermeded de Addison tratada con exito por la tuberculina). Saez de Santa Maria (R.), Méd. Ibera (Madrid), 1921, **14**, 19-21.

Clinical history of a patient with Addison's disease whose primary symptoms appeared after an attack of typhoid. The treatment consisted of opotherapy combined with tuberculin in progressive doses, following which occurred marked improvement. After four years' observation, says the author, the patient was able to consider himself clinically cured.—E. B.

Treatment of epilepsy by removal of an adrenal (Zur Behandlung von Krämpfen mit Exstirpation einer Nebenniere). Sändor (S.), Zentralbl. f. Chir. (Leipzig), 1921, **48**, 881-883.

Although the author operated in 4 cases the time elapsed is still too short to speak of definite results. Nevertheless, this operation may be tried in cases in which other treatment has failed.—J. K.

ADRENAL insufficiency (Formes cliniques et traitement de l'insuffisance surrénale). Sézary (A.), Presse méd. (Par.), 1919, **27**, 533-535.

Sézary classifies suprarenal insufficiency under three headings: the fulminating, rapidly fatal form; the monosymptomatic form (myasthenia or amyotrophy), and the form inducing a whole set of symptoms: acute (syndrome of Sergent-Bernard); subacute and slow (Addison's disease and its varieties). Tuberculosis may induce any one of these "syndromic forms" of suprarenal insufficiency, and syphilitic processes often locate in the suprarenals, as also those of diphtheria, typhoid and other acute infections. Specific treatment should be given when such is possible, antitoxin with diphtheria, for example, or quinin with malaria. Rest and suprarenal treatment are useful whatever the infection, but he prefers the extract of the whole gland, and given by the subcutaneous route. He reserves epinephrin for acute disturbances with collapse of the heart, and recommends the subcutaneous route. He gages the dose by the therapeutic results obtained with the first doses and by the signs of intolerance. A rise in the blood pressure is a good index of the efficacy of the opotherapy, but the fact that it does not rise does not prove that the treatment has been ineffectual. A still more instructive index is the finding with the dynamometer showing the variations in the strength

of the muscles tested fifteen and thirty minutes, one hour, three hours and so on after the injection of the suprarenal extract. When these two tests show a favorable influence from the suprarenal treatment, he keeps up this dose, not increasing it until the effect grows less pronounced. The appearance of tremor calls for caution; glycosuria, albuminuria, circulatory disturbances require suspension of this treatment. In some cases the doses have to be high and kept up for several weeks or even months before a good result is obtained. Signs of intolerance should be watched for with special care in these circumstances. Sometimes addition of **pituitary** will give surprisingly fine results when the suprarenal treatment is a failure. With cheesy tuberculosis and cancer, the knife is still the ideal treatment, possibly resecting only the pathologic tissues and leaving the rest intact. But in order that this can be done the disease has to be diagnosed early, and it is to be hoped that the progress of medicine will soon render this possible.—J. Am. M. Ass., **73**, 1399.

ADRENAL ablation in the treatment of genuine epilepsy (Die Nebennierenreduktion in der Behandlung der genuinen Epilepsie). Steinthal (C.), Zentralbl. f. Chir. (Leipzig), 1921, **48**, 878-881.

A report of seven cases operated upon without successful outcome. After the operation the blood pressure, blood picture, NaCl metabolism, carbohydrate tolerance, blood sugar and bilirubin content of the serum were unchanged. The acidity of the gastric secretion appears to have been slightly lowered.—J. K.

Is ADRENAL ablation justified in epilepsy (Ist die Nebennierextirpation bei Epilepsie berechtigt)? Specht (C.), Zentralbl. f. Chir. (Leipzig), 1921, **48**, 1347-1348; Deutsche med. Wchnschr. (Berlin), 1921, **47**, 1313.

When animals are inoculated with tetanus toxin fatal spasms occur which are identical whether one adrenal is removed or not. Fischer has stated that the removal of one adrenal diminishes the sensibility of animals towards amyl nitrite. As the animals show great individual differences in sensibility, Specht first estimated this sensibility before and after removal of an adrenal. Perhaps some small changes, but certainly no important increase of the resistance was observed. But even if Fischer's statements were true, the operation would be useless in epilepsy, since not only does the other adrenal show hypertrophy, but also the residue of the chromaphil tissue may also enlarge.—J. K.

Epinephrin hyperglycaemia. II. Tatum (A. L.), Pharmacol. & Exper. Therap. (Balt.), 1921, **18**, 121-131.

A study of the conditions under which epinephrin acts as a glycogenolytic agent. Epinephrin, as a glycogenolytic agent, has only

a transient existence in the circulating blood. Epinephrin glycogenolysis occurs only pari passu with the inflow of epinephrin into the blood, be it from subcutaneous or from direct injection. There is no essential difference between the glycogenolytic action of epinephrin given intravenously and given subcutaneously.—J. B. C.

Need of the physiological control of ADRENALIN and of preparations of the suprarenal glands. Tiffeneau (M.), J. pharm. chim. (Paris), 1921 (7), **23**, 313-317; 366-375.

A plea for the physical, chemical, and biological control of adrenalin and its preparations based on the variable results noted on testing, by a modified U. S. P. method, 5 commercial adrenalin solutions, and 5 preparations of the suprarenal glands.—Chem. Abst., **15**, 2336.

ADRENAL ganglioneuroma with testicular hypertrophy [Ein Ganglioneurom der Nebenniere (mit Hodenhypertrophie)]. Wassmund (C.), Virchow's Arch. f. path. Anat. [etc.] (Berlin), 1919, **226**, 319-332.

Wassmund found in the medulla of the right suprarenal of a man, aged 26, a tumor the size of a walnut, composed of sympathetic ganglion cells and nerve-fibres, medulated and non-medulated, which were tending to infiltrate the cortex of the gland.—Med. Sc. Abst. & Rev., **5**, 40.

(ADRENIN, THYROID) Sensitization for radio-activity by hormones (Sensibilisatie voor radioactiviteit door harmonen). Zwaardemaker (H.), Nederl. Tijdschr. v. Geneesk. (Haarlem), 1921, **65** (II), 794-796.

When the potassium is removed from Ringer's solution used to perfuse a frog's or mammal's heart, it ceases to beat. If potassium or another radio-active salt (uranium, radium) is added or exposure to radium rays is made, the heart again beats. The "radiobiological" dose was found to be much smaller during summer than during winter. He observed that the sensitivity to radio-activity is decreased by calcium, strontium, barium and perhaps thyroidine. It is increased by fluorescein, eosin, choline and adrenin. In summer 5 mgm. KCl to one litre of Ringer's solution must be present to make the heart beat. When, however, 0.001 mgm. of adrenin is added only 1 mgm. KCl is needed. The same amount of adrenin lowers the summer dose of uranium nitrate from 0.1 to 0.01 mgm. per litre. It is possible that the hormones are the regulators of the potassium radio-activity in the body.—J. K.

The importance of the AUTONOMIC nervous system in clinical medicine (De beteekenis van het vegetatieve zenuwsteloel voor de klinick). Koopman (J.), Handelingen van het XVIII de Neder-

landsch Natuur en Genneeskundig Congres (Haarlem), 1921, **18**, 146-148.

A general review without new facts.—J. K.

The pharmacology of the AUTONOMIC nervous system. Storm van Leeuwen, Handel. v. h. XVIII d. Nederl. nat.-en geneesk. Cong. (Haarlem), 1921, **18**, 148-151.

A critique on the theory of **vagotonia** and **sympathicotonia** according to Eppinger and Hess. The sensitivity of animals to pilocarpin, atropin, histamin and **adrenalin** is not at all changed after extirpation of **pancreas, thyroid** or **adrenals.** It is generally accepted that adrenalin stimulates the ends of the sympathetic, pilocarpin the myoneural junctions of the vagus. It has, however, never been proved that these substances have any relation to these nerves. If, in the book of Eppinger and Hess, every "vagotonia" is changed into "sympathicotonia" and every "sympathicotonia" into "vagotonia," the conclusions are just as logical as in the original version. Nearly all persons who have a special sensitivity to adrenalin have practically the same to pilocarpin. It is perhaps possible that there exist patients who have all the symptoms of vagotonia, but all the relations between these symptoms and the functions of adrenals or thyroid have not yet been proved. The pharmacological way of diagnosing vagotonia seems to be perfectly useless.—J. K.

(TETANY) The importance of the calcium-ion concentration for the existence of spasmophilic symptoms (De beteekenis van de concentratie van vije calciumionen voor het ontstaan van spasmophile verschijnselen). Van Paassen (P.), Nederl. Tijdschr. v. Geneesk. (Haarlem), 1921, **65**, 1162-1171.

It is a fact, admitted by all investigators, that calcium plays an important part in the pathogenesis of tetany. The total amount of calcium present in the blood is not as important as is the quantity of free calcium, which is intimately related to the irritability of the nervous system. This concentration depends mainly on the concentration of the bicarbonate-ions. When the total amount of calcium increases $Ca(HCO_3)_2$ is formed which gives rise to a momentary decrease of concentration of bicarbonate-ions. The determination of the total of free calcium-ions is advocated as a clinical procedure. When the concentration of Ca-ions is decreased nervous irritability rises, though a real attack of tetany has never been observed in the author's experiments. Calcium is certainly not the only important factor in the pathogenesis of tetany.—J. K.

(CORPUS LUTEUM) Experimental studies of oval implantation and development in the uterus (Experimentelle Studien über die Einnistung und Weiterentwicklung des Eis im Uterus). Biedl

(A.), Peters (H.) & Hofstätter (R.), Ztschr. f. Gebs. u. Gyn. (Stuttgart), 1921, **84**, 59-130.

This is a noteworthy contribution to the subject of the implantation of the egg and its development within the uterus. Its length and detail preclude an adequate abstract. The observations indicate that the corpus luteum may participate in the phenomenon.—F. S. H.

Experimental studies in DIABETES. Series II. The internal pancreatic function in relation to body mass and metabolism. II. Changes in assimilation by alteration of body mass. III. The effects of exercise. IV. Pancreatic cachexia. Allen (F. M.), Am. J. M. Sc. (Phila.), 1921, **161**, 16-32; 165-193; 350-364.

In considering the second paper of this series these relations were investigated in obese dogs, by a study of the alteration of body weight in the same animal and the alteration in the body mass in the form of active protoplasm. The conclusions drawn are that the assimilative power of diabetic animals rises and falls inversely with the body weight. This change is established on different diets, which excludes the supposition that it is due merely to variations in either glycogen or protein, and which proves that it is produced also by the feeding and deposit of a non-sugar forming material, namely, fat. When considerable masses of active tissue, especially muscle, are removed by amputation, the effects upon the assimilation are negligible compared with those of similar losses of weight produced by undernutrition. It may therefore be concluded that the effects of undernutrition are not due to a reduction of active protoplasm but rather to a reduction of food supplies and metabolism. The pancreatic function is spared when the same number of cells metabolize a reduced quantity of food materials. This principle is important clinically in that undernutrition should be continued to the point of relieving the pancreatic function from overstrain revealed by the most delicate tests, particularly hyperglycemia. The present investigation has aimed at the valid proof of a quantitative relation between the internal pancreatic function and the total body weight and metabolism. Any theories of the nature of this function or of diabetes must take account of the fact that the islands of Langerhans are concerned not merely in the combustion of sugar or storage of glycogen, but also in the maintenance of the general tissues and reserves. In some manner an increased supply of fat or formation of adipose tissue imposes a burden on the island function, and reduction of any kind of food or of the body weight reduces the demand upon this function. This fact seems to indicate that the island hormone has both a catabolic and an anabolic role.

In the third paper of this series the influence of carbohydrate assimilation was traced from the normal through various stages of impairment. A rise of plasma sugar, presumably representing increased transportation, ordinarily accompanies exercise in the normal

animal, and the assimilation for test doses of glucose is increased. In mild diabetics, when there is a tendency to abnormal hyperglycemia from defective assimilation of carbohydrate, exercise markedly diminishes the hyperglycemia and glycosuria and facilitates utilization. This power of exercise to improve assimilation applies to the glucose formed from protein diets or body stores as well as from preformed carbohydrate. It does not depend upon the febrile temperatures which attend heavy exercise in dogs, for equal results were obtained in human patients without important elevations of temperature. It is not lost with long usage, but becomes less as the diabetes becomes more severe. At a certain advanced stage exercise is unable to modify hyperglycemia or glycosuria. Beyond this, in the extreme forms of diabetes in partially depancreatized animals and in totally depancreatized animals, the extra mobilization of sugar by exercise results in an actual increase of glycosuria and of the D:N ratio.

In the clinical application, dependence for the actual control of the diabetes is placed upon diet, and exercise is limited to the requirements of comfort and hygiene. The thorough dietetic treatment thus involves two changes from former practice: on the one hand heavy exercise as advocated by the earlier clinicians for burning up surplus sugar is discouraged; on the other hand, the hygienic benefits of lighter exercise are made available to many patients to whom exercise was formerly forbidden.

Continuing this in the fourth paper, Allen reports his observation on the acute deaths from unknown cause after partial pancreatectomy. Examples of diabetic asthenia, diabetic gangrene in animals as well as examples in which the diabetes of dogs and cats was replaced by a fatal cachexia of unknown origin are given. He considers the diabetic asthenia and gangrene as due to specific endocrine deficiency. He emphasizes the importance of distinguishing mere suppression of glycosuria by some injury, poison, or cachexia, from genuine control or improvement of the diabetes.—J. F.

The management of certain types of DIABETES MELLITUS. Branton (W. B.), Virginia Med. Mo., 1921, **48**, 267-271.

The author points out that diabetes mellitus should be recognized by the routine examination of the urine and the blood for sugar before symptoms arise. He calls attention to the faint yellow reactions got in doing Fehling's test on mild diabetics. Some of the problems of handling the obese diabetic are pointed out. The usual method of rendering such cases sugar free is shown. The difficulty of reducing such a patient's weight, the seriousness of a persistent ferric chloride reaction, and the level to which one should attempt to reduce the blood sugar often present unanswerable problems. The difficulty of treating diabetes complicated by tuberculosis is dwelt upon. Allen's treatment was used in four cases; the results were

not encouraging. Finally, old age should not debar any patients from the benefits of modern dietetic treatment. They should be rigidly kept to their allowance of food, though all changes in their former habits should be made slowly and with extreme care. Cases illustrating each point are reported.—Author's Abst.

Atropin in DIABETES (Atropin bei Diabetikern). Bornstein (A.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 1200-1201.

Substances which stimulate the parasympathetic increase the quantity of blood sugar. This has been proved for pilocarpin, physostygmin, cholin and acetylcholin. When atropin is first given these substances have no effect. In about 25 per cent of the cases of diabetes, atropin causes a decrease of blood sugar.—J. K.

DIABETIC acidosis. Edgar (T. W.), Med. Rec. (New York), 1921, **99**, 952-954.

The author is not an enthusiastic advocate of the starvation treatment in diabetes mellitus, believing that many patients become too undernourished, weak, and economically unfit. He does not seem to consider "getting the urine free from sugar" the goal to be striven for in most cases. "Many patients are worse off with a sugar free urine than others whose sugar content is high." His treatment for acidosis is then outlined, depending upon whether the patient is in coma or not. Essentially it consists in the administration of carbohydrate by mouth or as glucose per rectum or intravenously, together with alkalies. In the treatment of diabetics, body weight should be preserved unless, of course, the patient is obese. He believes the thin and cachectic develop acidosis more readily. He has never seen one gaining or maintaining his weight develop coma.
—H. L.

(DIABETES) Alimentary hyperglycemia and glucosuria (Zur alimentären Hyperglykämie und Glycosurie). Eisner (G.) & Forster (O.), Berl. klin. Wchnschr., 1921, **58**, 839-842.

Hyperglycemia may exist without glucosuria, glucosuria may exist without hyperglycemia. The explanation that in these cases the kidney is more or less permeable for sugar is no explanation, but simply states the problem in other words. The authors give 150 grams of white bread to many persons when fasting. The blood sugar frequently rises about 100 per cent on this diet. Here a most interesting fact was observed. In one patient 100 grams of saccharose was given on the empty stomach. The blood sugar rose from 0.115% to 0.186% and glucosuria occurred. In the same patient the injection of 1 mgm. of **adrenalin** caused a rise of the blood sugar to 0.2% with glucosuria. After 100 gm. of wheat flour and 100 gm. of white bread the blood sugar rose to 0.18%, but no glucosuria was observed.

It is often possible to obtain by bread feeding the same amount of blood sugar as by the injection of adrenaline. In the first case, however, no glucose is found in the urine, while in the second glucosuria is quite common. The greatest increase in blood sugar after administration of bread is seen in persons with an increased irritability of the involuntary nervous system or in patients with a hyperfunction of the **chromaphil tissue.** Often the rise of the blood sugar begins as soon as the first pieces of bread have only just been ingested. The authors suggest that in these cases a nervous impulse from the stomach goes to the liver, which then mobilizes the sugar. If this is true, alimentary hyperglycemia may be compared to piqûre hyperglycemia. We know nothing about the relation between hyperglycemia and glucosuria. It is, however, probable that the occurrence of glucosuria depends on the intensity of the rise of the blood sugar and on its duration.—J. K.

(DIABETES) Phosphates and blood sugar (Phosphatinjektion und Blutzucker). Elias (H.) & Weiss (St.), Berl. klin. Wchnschr., 1921, **58**, 959-960.

In normal persons intravenous injections of solutions of NaH_2PO_4 or Na_2HPO_4 had no influence whatever on the blood sugar, though they decreased alimentary hyperglycemia. In diabetics hyperglycemia was nearly always diminished by these injections. It was possible to prove that the sugar was not excreted in another way, for instance as levulose-biphosphate.—J. K.

Practical and historical observations on the "Mehlfrüchtekur" in DIABETES mellitus (Praktisches und Historisches zur Mehlfrüchtekur bei Diabetes mellitus). Falta (W.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 889-891.

Falta calculates that 100 grams of protein may produce about 80 grams of sugar. It is, therefore, possible to give the quantity of allowed food, partly as protein and partly as carbohydrates when the tolerance for carbohydrates is known. In cases with acidosis more carbohydrate, in other cases more protein must be given. Not all proteins and not all carbohydrates can be given with the same success. Generally when small quantities of protein are given an increased amount of fat in the diet has no influence on the excretion of sugar or fat. There are patients with diabetes who have a special sensibility against proteins, others are very sensitive towards carbohydrates. A diet rich in calories but poor in proteins should be tried.
—J. K.

Retention of protein during diet reduction to relieve the glycosuria in DIABETES MELLITUS. Fenlon (R. L.), Am. J. M. Sc. (Phila.), 1921, **161**, 193-203.

Fenlon now reports forty cases treated by this method and outlines the details of the method and instructions together with illustrative case histories. It consists essentially of maintenance of the protein intake at a moderate level, restriction of fat and relatively rapid reduction of carbohydrate until the patient's glycosuria disappears. The carbohydrate tolerance is then built up by a gradual increase in the carbohydrate intake.—J. F.

Studies on blood sugar. The total amount of circulating sugar in the blood in DIABETES mellitus and other conditions. Fitz (R.) & Bock (A. V.), J. Biol. Chem. (Balt.), 1921, **48**, 313-321.

The plasma of blood from diabetic persons contains relatively more sugar than do the corpuscles. This suggests that the plasma in diabetes is a vehicle for the transportation of sugar from the body cells, which are unable to burn or store it, to the kidney which excretes it, and that the blood corpuscles are but little concerned with such transportation of sugar. Glucosuria does not occur unless the plasma sugar exceeds a certain threshold. Blood sugar concentration expressed as milligrams per 100 cc. of blood or plasma may give misleading information with regard to the total amount of circulating sugar. The threshold at which glucose appeared in the urine of the diabetic patient of this series seemed to lie between 5.20 and 5.36 grams of total plasma sugar.—F. S. H.

(DIABETES) Symptoms and treatment of coma diabeticum (Symptomatologie und Therapie des Coma diabeticum). Forschbach (J.), Ztschr. f. ärztl. Fortbild. (Jena), 1921, **18**, 421-427.

A general review without new data.—J. K.

The administration of roasted carbohydrates to patients with DIABETES (Ueber die Ernährung von Zuckerkrankem mit stark gerösteten Kohlehydraten). Grafe, Deutsche med. Wchnschr. (Berlin), 1921, **47**, 1080.

Data reported elsewhere.—J. K.

Feeding DIABETICS with roasted carbohydrates (Die Ernährung der Diabetiker mit gerösteten Kohlehydraten). Grafe (E.), München. med. Wchnschr., 1921, **68**, 827-829.

Grafe points out that, as caramel may be of great use in the treatment of diabetes, it was desirable to try roasting of other carbohydrates. It is possible by adding much fat to make tasteful food from roasted rice, potatoes, porridge, oats, bread, etc. The glucosuria, produced by these substances, is four to ten times less after than before roasting.—J. K.

(DIABETES) The apparent influence of a diet of carbohydrates on the pancreas remnant of partially pancreatectomized dogs. Jensen

(V. W.) & Carlson, (A. J.), Am. J. Physiol. (Balt.), 1920, **51**, 423-429.

After the removal of approximately 88% of the pancreas gland a liberal carbohydrate diet tends to change diabetes levis into diabetes gravis. The authors question the soundness of the theory that fasting relieves diabetes in man by removing "overstrain" from an impaired pancreas. There was practically no hypertrophy of the pancreas remnant when its functional capacity had been reduced to a point below its ability to prevent diabetes—Chem. Abst.

Formation of antibodies and INTERNAL SECRETION (Vorming van tegenstoffenen inwendige afscheiding). Koopman (J.), Nederl. Tijdschr. v. Geneesk. (Haarlem), 1921, **65**, 3489-3495.

A review of the literature on this subject. No new data.—J. K.

DIABETES und Chirurgie. Krecke (A.), München. med. Wchnschr., 1921, **68**, 887-888.

A general review. When an operation is absolutely necessary (ileus, hernia incarcerata) diabetes should not be regarded as a contraindication, but when there is a possibility of favorable outcome with internal treatment, e. g., in appendicitis without peritonitis, operation ought not to be carried out in a diabetic patient.—J. K.

Transitory DIABETES after mumps (Diabète transitoire post-ourlien). Labbé (M.) & Debré (R.), Bull. et mén. Soc. méd. des Hôp. d. Par., 1921, **45**, 1306-1309.

A report of a case of hyperglycemia following pancreatic mumps. —F. S. H.

Practical treatment of DIABETES (Die praktische Behandlung des Diabetes). Lange (J.), München. med. Wchnschr., 1921, **68**, 1002.

In the United States it seems, according to Lange, a not infrequent mistake to make a diagnosis of diabetes in cases of pentosuria. Pentosuria is not rare in America, which is due to the frequent use of fruit wines. Most doctors are too afraid of acetone. If a patient excretes 1-2 grams of acetone daily, even with diacetic acid, there is no danger of coma. Treatment consists mainly in avoiding overeating, and reducing the large quantities of animal protein. A systematic treatment in a sanatorium should be recommended.—J. K.

Syndrome of compression of the cavernous sinus accompanied by DIABETES INSIPIDUS and "basedowification" of a goiter (Syndrome de compression de sinus caverneux, avec diabéte insipide et basedowification d'une goitre). Ledoux (E.), Bull et mém. Soc. méd. d. hôp. de Par., 1921, **45**, 827-830.

Presentation of a case as described in the title. Polyuria was present, which yielded to the injection of posterior lobe extract. The patient recovered from all his troubles spontaneously. The disturbances are attributed to an enlargement of the posterior lobe of the hypophysis.—F. S. H.

DIABETES MELLITUS, syphilis, and the negro. Lemann (I. I.), Am. J. M. Sc. (Phila.), 1921, **162**, 226-230.

This study is based on the experience of the Charity Hospital at New Orleans. From 1898-1909, 61,298 admissions included 45 white and 19 negro diabetics. Although the negroes furnished 40 per cent of admissions, they gave only 30 per cent of the diabetics. From 1910-1919, inclusive, there were 160,044 admissions in which there were 135 white and 59 negro diabetics. Here the negroes furnished 43 per cent of the admissions and only 30 per cent of the diabetics. The negro furnished at the same time more than 50 per cent of all the syphilitic diseases. So the author concludes there is no relation between the incidence of diabetes mellitus and syphilis. Hence there is no probable etiologic relation between the two. Further, there is an unexplained immunity in the negro race to the production of spirochetal pancreatitis just as there is an unexplained immunity of the race to the production of locomotor ataxia.—J. F.

The treatment of DIABETES (Zur Therapie des Diabetes mellitus). Lenné, Deutsche med. Wchnschr. (Berlin), 1921, **47**, 867-868.

According to the author, it is nowadays "fashionable" to give diabetics as little protein as possible. He considers this in general a mistake and believes that many cases of acidosis and coma are due to low protein diet. In coma administration of alkali never is successful. When carbohydrate treatment is employed it is necessary to individualize. There are patients who do better on a potato diet, while oatmeal gives no success. In others the effect of oatmeal is splendid and potatoes have a bad influence. Caramel, that has again been recommended in Germany, not only has a bad taste, but, though it does not increase glucosuria, fails likewise to decrease acidosis. Cocoa and chocolate may be very useful. Bitter chocolate containing little sugar often proves of much value in completing the diet.
—J. K.

Treatment of DIABETES (De praktijk der diabetesbehandeling). Lubbers (H. A.), Nederl. Tijdschr. v. Geneesk. (Haarlem), 1921, **65 (II)**, 1841-1846.

A general review of the treatment of diabetes. With the Allen-Joslin method as well as with Falta's "Mehlfrüchtekur" good results may be obtained. Individualization is necessary.—J. K.

A study of DIABETES INSIPIDUS (Beitrag zur Lehre von Diabetes insipidus). Meyer (E.) & Meyer-Bisch (E.), Deutsch. Arch. f. klin. Med. (Leipzig), 1921, **137,** 225-233.

A girl of 18 who was very nervous suddenly developed polydipsia and polyuria. The average urine output was about 10 liters daily. Skiagrams of the skull showed no changes. When water was withheld for 6 hours the patient complained of palpitations and severe headache. The urine output during these 6 hours was 2080 cc. The NaCl concentration of the blood rose from 0.645% to 0.71%. The concentration of the urine rose from 0.04% to 0.12%. These facts prove the case to be one of real diabetes insipidus and, according to Veill (See Endocrinol., 1919, **3,** 195), a hyperchloremic case of this disease. The effect of pituitrin was very marked. It was injected for a period of 8 days; the NaCl content of the blood became 0.58%. The authors tried to find out whether pituitrin acts only upon the kidneys or also on the tissues. A canule was introduced into the ductus thoracicus of a dog and the lymph collected. Injection of pituglandol decreased the quantity of lymph; the protein and NaCl concentration were increased. After the injection the blood at first was slightly diluted, but later the concentration of hemoglobin, erythrocytes and serum protein became higher. These two facts prove that pituglandol increases the property of the tissues to retain water. Pituitrin thus has a double effect, one on the tissues and one on the kidneys.—J. K.

(DIABETES) The ammonia content of the blood, and its bearing on the mechanism of acid neutralization in the animal organism. Nash (T. P.) & Benedict (S. R.), J. Biol. Chem. (Balt.), 1921, **48,** 463-488.

It would appear as if in diabetes there is an introduction into the blood stream of acid radicles more rapidly than the normal kidney can eliminate them, or can make ammonia to combine with them while eliminating them.—F. S. H.

Modern treatment of DIABETES (Ueber der jetzigen Stand der Diabetestherapie). v. Noorden (C.), München. med. Wchnschr., 1921, **68,** 1064.

The underfeeding treatment must not be exaggerated. Though carbohydrate treatment is extremely useful, especially in cases with acidosis, the "Mehlfrüchtekur" as described by Falta cannot be recommended, since this diet contains too small amounts of proteins. An intelligent diabetes diet must change from time to time. A diet rich in proteins and poor in carbohydrates, and another rich in carbohydrates and poor in proteins may be used alternatively.—J. K.

Vegetable problems in DIABETIC diets. Orton (W. A.), Am. J. M Sc. (Phila.), 1921, **162,** 498-509.

A most interesting discussion by an agriculturist of the food supply of the diabetic. A list of vegetables for a "diabetic garden" is given. The author grew this year 81 species in 255 varieties and has accomplished the aim of having some fresh green vegetables of his own growing every day in the year without a greenhouse.—J. F.

Ear complications in DIABETES (Complicazioni otitiche in diabetes). Perrone (P.), Il Morgagni (Milano), 1921, **64,** 178-196.

Report of the complications of purulent otitis media, and meningitis purulenta in diabetes. The author concludes that it is not justifiable to wait till all symptoms are present, but the operation should be performed as soon as possible. If, however, it is possible two or three weeks before the operation, anti-diabetic treatment should be instituted; this will largely diminish the risks of the operation. The operation should be carried out under light ether narcosis or under local anaesthesia. The operating should be done as quickly and simply as possible. Both the mastoid and dura mater should receive due attention in the operation.—J. K.

DIABETIC coma and convulsive crises. Acidosis and meningeal hemorrhage (Coma diabétique et crises convulsives. Acidose et hémorragie méningée). Rathery (F.), Cambessedès & Welti, Bull et mém. soc. méd. des hôp. de Par., 1921, **45,** 1265-1268.

Report of a case as described in the title.—F. S. H.

Urine in DIABETES MELLITUS. Richards (J. H.), N. York State J. M., 1918, **18,** 193.

There may be an increased excretion of NH_3 in the absence of urinary acetone bodies, and a normal excretion of NH_3 in their presence. The quantity of sugar excretion has no relation to the N distribution of the urine. In many cases there is a N disturbance which may be corrected by regulating the N intake, but no correction of urinary nor acetone bodies will correct this N disturbance.—Physiol. Abst., **3,** 434.

Researches on DIABETES (Beiträge zur Diabetesforschung. I, II, III, IV.) Sakaguchi (K.), Mitt. a. d. Fakult. d. k. Univ. zu Tokyo, 1918, **20,** 345-373; 439.

Sakaguchi reports an exhaustive study of various features of diabetes. He discusses why the tolerance of diabetics is the lowest at breakfast and the elimination of sugar the highest after this meal. His conclusion is that this is due to the fact that the production of glycogen is less after breakfast than at other meals. The elimination of sugar after breakfast can be reduced by giving a little carbohydrate or meat an hour or two before the breakfast. He states further that carbohydrates to the limit of tolerance are borne better

if taken four or five hours after the preceding meal. When the interval is six hours or more, the glycosuria may be increased. Clinical evidence is presented to show the injurious action of emotional stress on the sugar content of the blood, while brain work, without emotional disturbance, does not modify the glycemia. In the three cases described, the sugar content of the blood was determined before and after the patients had been informed of the serious nature of their disease. Diabetics should avoid occupations, he suggests, that entail worry or excitement. The fourth communication discusses the influence of intake of albumin on the sugar content of the blood. As the considerable rise in the sugar content reaches its highest point in from two to four hours after eating meat, it seems to be due to the products of digestion in the small intestine, rather than to the products of putrefaction of albumin in the large intestine.
—J. Am. M. Ass.

(DIABETES) Cholesterin in blood serum (Ueber den Cholesteringehalt des Blutserum bei Krankheiten). Stepp (W.), München. med. Wchnschr., 1918, **65**, 781-785.

A increase occurs in diabetes, certain liver diseases and nephritis.—Physiol. Abst., **3**, 576.

(DIABETES) Critical analytical discussion and experiments in the determination of the blood sugar in health and disease (Kritisch analytische Betrachtungen und Untersuchungen zur Bestimmung des wahnen Blutzuckers bei Gesunden und Kranken). Stepp (W.), Arch. f. exp. Path. u. Pharm. (Leipzig), 1921, **90**, 105-128.

In estimating the amount of blood sugar it is necessary, when working with a reduction method, to remove not only the proteins but also other substances with reducing properties such as uric acid, creatinin, and amino acids from the serum. Mixing the serum with phosphotungstic acid is a better method than the use of colloidal iron oxide. When the blood sugar is estimated after precipitation with phosphotungstic acid and evaporation the amount of reducing substances is diminished. The best way to determine the blood sugar is by polarization or fermentation. The results of the reducing methods are 40 to 100 per cent too high.—J. K.

DIABETES INSIPIDUS. Umber, Deutsche med. Wchnschr. (Berlin), 1921, **47**, 763.

A demonstration of a patient with polyuria, headaches, hemianopsia. No change in the sella turcica was found. The Wassermann reaction was strongly positive. Antisyphilitic treatment gave good results, and the eye symptoms disappeared completely.—J. K.

The retinitis of DIABETES MELLITUS. Wagner (H. P.) & Wilder (R. M.), Collected Papers of Mayo Clinic, 1920, **12**, 756-761. (Reprint from J. Am. M. Ass., **76**, 515-517).

From an intensive study of the cases of diabetes at the Mayo Clinic the authors conclude that the primary cause of the retinitis of diabetes lies in the accompanying pathologic changes in the vascular system.—J. F.

Plasma chlorides and edema in DIABETES MELLITUS. Wilder (R. M.) & Beeler (Carol), Collected Papers of Mayo Clinic, 1920, **12,** 398-405.

Data are presented to show that edema in diabetes differs fundamentally from the edemas in diseases of the heart and kidneys. The determining factor seems to be inanition, which relates it to the hunger edema of war times and the other edematous condition of undernutrition.—J. F.

(DIABETES MELLITUS) An evaluation of the Allen method of treatment. Williams (J. R.), Am. J. M. Sc. (Phila.), 1921, **162,** 62-72.

A report of the application of this method to 103 cases treated in the author's clinic since 1915. He concludes that the Allen treatment is a distinct clinical advance. In the majority of cases its value is in inverse proportion to the seriousness of the failure of metabolism. The treatment is of little avail when serious infections are present or when the patient is afflicted with the degenerative processes of old age. Many patients find the treatment too exacting. A very considerable proportion of those who die from diabetes are patients with severe cases who willfully violate their diets and rapidly succumb. Fewer than 14 per cent were persistently faithful to the treatment. Many die because of lack of courage. Patients with serious or hopeless complications frequently abandon dietary treatment. Often in adults death resulted because of the inability of the patients to provide suitable care. Neglected diabetes is more rapidly and certainly fatal in a child than in an adult. The majority of patients who live within their food tolerance gain in physical vigor; furthermore, the distressing symptoms incident to the disease noticeably lessen. Moderately severe cases do surprisingly well. Severe cases which have not been rigidly dieted are markedly benefited by the institution of the Allen treatment. Patients who have been dieted carefully for long periods do less well. Kidney functional tests in thirty-nine cases after the administration of thirty doses of arsphenamin, each dose consisting of 4.6 g. and distributed over a two-year period failed to give any conclusive evidence of injury to the kidneys.—J. F.

Examination of the blood in DIABETES mellitus. Williamson (R. T.), Practitioner (London), 1921, **107,** 169-173.

The author describes his method for estimating the sugar content of the blood, originally published in 1896. It is useful in detecting marked increase above normal blood sugar value, but is not available for estimating slight changes. Only one large drop of blood is required. This is an advantage, and the procedure is so simple that it may be performed at the bedside. The author himself remarks that other blood tests are necessary and desirable for indicating the exact percentage of sugar.—H. L.

The relation of the DUCTLESS GLANDS to gynecology: physiological and therapeutic. Bigelow (Alice H.), Boston M. & S. J., 1918, **178,** 715-718.

A classification of the endocrine glands is given on the basis of those which accelerate and those which retard metabolic processes. The former group includes the **thyroid, ovaries, testicles,** posterior lobe of the **pituitary,** and the medulla of the **adrenal.** The opposite group embraces the **parathyroid,** anterior lobe of the pituitary, suprarenal cortex and probably **thymus** and **pineal.** Among the gynecological applications of endocrine knowledge and therapy briefly discussed are the atrophy of the thymus at puberty; the exaggeration of secondary sex markings with acromegaly, and the genital retrogression of hypopituitarism; the amenorrhea often seen with thyroid disorders and with pituitary insufficiency. The article concludes with a short discussion of ovarian therapy in such conditions as the above.—E. N.

(ENDOCRINE) On fits, epileptic and others. Feiling (A.), Practitioner (London), 1921, **107,** 22-32.

The author presents a classification of "epileptiform fits" according to etiology and it is interesting to note that no mention of so-called **pituitary** or **ovarian** epilepsy is therein made. However, toward the end of the article the following sentence occurs: "The frequent association in women of epileptic fits with menstrual periods raises the question whether some biochemical or **endocrine** factor may be the cause."—H. L.

The relation of eclampsia to the ENDOCRINE ORGANS of the child (Die Bezeihung der Eklampsie zum endokrinen Drüsensystem des Kindes). Fraenkel (M.), Zentralbl. f. Gyn. (Leipzig), 1921, **45,** 929-930.

Many years ago the author described a case of eclampsia in the 7th month of pregnancy. At post-mortem the child showed a large **thyroid** and a small **thymus.** He now reports two similar cases (no details are given) and believes that the endocrine system of the mother takes the place of the endocrine system of the child. The primary cause of eclampsia is probably, in his opinion, endocrine

insufficiency of the child. (As no clinical details are given it is difficult to decide whether this little article is as full of nonsense as it appears.)—J. K.

(ENDOCRINE) The ductless glands and constitutional diagnosis. Gutman (J.), Med. Woman's J. (Cincin.), 1920, **27**, 281-286.

See Endocrin., **4**, 624.

(ENDOCRINE GLANDS) Glandular dystrophies and particularly mono-symptomatic dystrophies (Dystrophies glandulaires et particulièrment dystrophies mono-symptomatiques). Hutinel (V.) & Maillet (M.), Ann. de méd. (Paris), 1921, **10**, 89-114.

A lengthy discussion in which total dystrophies or endocrine cachexias, such as myxedema, cretinism, cachexia strumipriva and pachydermal cachexia are considered together with **adrenal** and **hypophyseal** dysfunctions. General systematized dystrophies are considered as in a class by themselves, examples of which are various **hyper-** and **hypo-thyroid** states, acromegaly, gigantism, nanism, the adiposo-genital syndrome, adrenal pseudo-hermaphroditism, adrenal virilism and hirsutism. In fact, the whole range of disorders rightly or wrongly attributed to disturbances of function of single endocrine glands is succinctly reviewed in a masterly fashion.—F. S. H.

Pathology of the ENDOCRINE organs (Zur Pathologie der Endokrinen Drüsen). Löhlein, München. med. Wchnschr., 1921, **68**, 1036.

A short note. In a case of osteitis fibrosa an adenoma of one **parathyroid** was found. In a boy of 15 with infantile **testicles** and absence of secondary sexual characters with a slight degree of adiposity a teratoma of the **pineal** was found. The author believes this to be a case of dystrophia adiposo-genitalis from hydrocephalus with pressure on the pars posterior of the **hypophysis.**—J. K.

(ENDOCRINE ORGANS) Osteomalacia and hereditary lues (Osteomalacia y heredo-lues). Malamud (Teresa), Prensa Méd. Argent. (Buenos Aires), 1921, **7**, 264.

Report of a case diagnosed as osteomalacia, which was attributed to hereditary syphilis producing a pluriglandular syndrome.
—B. A. H.

New questions on the ENDOCRINE GLANDS (Neue Fragestellungen in der Lehre von der inneren Sekretion). Münzer, Fortschr. d. Med. (Berlin), 1921, **39**, 765-767.

The "new" observations of Münzer are rather old. He states that endocrine diseases are nearly always polyglandular. He believes that it is possible to express polyglandular diseases by mathematical

formulas: e. g., **Acromegaly**=Hyperfunction of **hypophysis** plus hyper- or hypo- (!!) function of **thyroid** plus hyperfunction of adrenals plus hypofunction of gonads plus hyperfunction of thymus (?). It is not necessary that a disease begin in the gland that is the chief etiologic factor of this disease. Acromegaly can perhaps just as well begin with a hypofunction of the **testicle** as with hyperfunction of the hypophysis. (The abstractor ventures to hope that this algebraic endocrinology will not be the beginning of a new series of nonsensical pronouncements on the physiology of the endocrine organs.)—J. K.

ENDOCRINE disturbance in mental defectives. Murdock (J. M.), Penn. M. J. (Harrisburg), 1921, **25**, 50.

The author reports that a considerable proportion of mental defectives show evidence of internal secretory disorders, mostly **hypothyroidism** or **hypopituitarism.** The mental defect is not necessarily the result of the glandular dysfunction; both may be due to an underlying cause. These changes frequently originate early in childhood. A plea is made for early recognition so that appropriate therapy may be instituted at a time when improvement is possible. After definite somatic changes have taken place, treatment is more difficult and less promising. In 100 autopsies of feeble minded patients reported by Raeder of the Massachusetts State Psychiatric Institute, 76% showed endocrine anomalies.—H. L.

ENDOCRINOLOGY. Noyons (A. K.), Vlaamsch. Geneesk. Tijdschr. (Ghent), 1921, **2**, 385-392.

A general review, without new facts. Some statements are rather doubtful. The "adrenal" is called the perfect type of an endocrine gland. It is stated that removal of the adrenals in an animal is not an important operation.—J. K.

Modifications in the ENDOCRINE GLANDS and in the blood of the chicken following the injection of adrenalin and of cholin (Modificazioni nelle glandole endocrine e nel sangue dei polli iniettati con adrenalina e colina). Pighini (G.), Biochim. e. Terap. Sperim. (Milano), 1921, **8**, 140-154.

The chickens experimented upon were between 2½ and 18 months of age. The adrenalin (1:1000) was used hypodermatically, endomuscularly and sometimes intravenously in doses of 1 cc. The cholin used was the hydrochlorate (Meck) 1 per cent in doses of ½-1 cc., either hypodermatically or intravenously. Besides the behavior of the blood, the following organs were studied: brain, **hypophysis, thyroid,** liver, spleen, **pancreas, adrenal** glands, kidney, **testis, ovary.** As regards adrenalin, the younger subjects offered less resistance, but all showed a great deal of adaptation to the drug, after

the first doses, as shown by their behavior and by autopsy findings. The organs, which showed a constant, well accentuated reaction, were thymus, spleen, adrenal glands and blood. Interesting effects of cholin on thyroid were also seen. As an effect of adrenalin parenchymal degeneration of the thymus occurred characterized by extreme reduction of the lymphatic elements of the cortex, of the corpuscles of Hassall and lipoid degeneration of the epithelial elements. An accentuated reduction of the Malpighian elements in the spleen and hypertrophy of the chromaphil tissue in the adrenal glands, accompanied by diminution of lipoids in the cortex, were seen. The blood showed a neutrophilic leukocytosis, The effects of cholin on the thymus were increased function and hypertrophic characteristics of the medulla, increased number of Hassall's corpuscles, numerous forms of hypertrophied epithelioid cells—myoid and giant—and colloidal cysts. In the thyroid hyperplastic changes were noted. Hypertrophy of the Malpighian corpuscles and tendency to hypertrophy of the interrenal tissue was seen in the spleen and in the blood, slight polynucleocytosis. The author insists that, while the thymus is always found hypertrophied and hyperactive after cholin administration, the thyroid appears hyperplastic. These two changes do not seem accidental, but might be referred to the relations between thyroid and thymus postulated in Basedow's disease. The data are taken to indicate a decided antagonism between adrenalin and cholin. This is being further studied.—G. V.

The relation of ENDOCRINOLOGY to vegetative or visceral neurology. Pottenger, (F. M.), N. York M. J. (New York), 1921, **113**, 364-366.

All smooth muscle and all secreting glands are innervated by vegetative nerves and activated by the products of the glands of internal secretion. The internal secretions act through or with one or the other division of the vegetative system, either as a whole or in some part of its distribution, hence vegetative functions, whether controlled through nerves or through internal secretions, can be divided into those which depend upon the sympathetic and those which depend upon the parasympathetic nerves for their activity. The sympathetics have for their function the defense of the body, while the parasympathetic system controls the intake and digestion of food. Disease interferes with the normal functions of defense and self-preservation, i. e., sympathetic and parasympathetic functioning. The individual will be able to execute these two outstanding purposes upon which his life depends in accordance with the stability or instability of his vegetative nervous and endocrine systems.—H. W.

The relation of the ENDOCRINE system to the glycemic reaction following the injection of homologous protein. Rohdenburg (G. L.) & Krehbiel (O.), Am. J. M. Sc. (Phila.), 1921, **162**, 28-40.

The authors report the effect of ablation of one or more glands of internal secretion upon the glycemic reaction. Albino rats were used. Blood sugar determinations were made by the method of Epstein. In a series of seventy normal, fully grown, healthy rats the blood sugar values were determined before and after injection of homologous protein. A variation between the preinjection sample and that taken 60 minutes after injection of 16 or more mgm. was taken as a positive reaction. In this series it was found that 73 per cent gave a positive reaction and that the average difference was 29 mgm. In the first experiments, a single "internal secretory" gland was removed. The glands entirely removed individually were the **spleen, thymus,** both **testes,** both **ovaries,** both **adrenals;** approximately 90 per cent of the **thyroid** and embedded parathyroids; and approximately 90 per cent of the pancreas. There were six animals in each group. In the second experiments, double ablations were performed in such rotation that all possible combinations were obtained, for example, testes-spleen, testes-thyroid, testes-adrenal, testes-pancreas. In each of these groups there were also six animals. There were two combinations of organs which, when ablated, inhibit the glycemic reaction; (1) spleen and either gonad set; (2) adrenal and pancreas. If one gland from either system be ablated and with it one gland from the other system, there results little or no change from the normal reaction. If, however, one gland from one system be removed with one gland from the other system, and, in addition, either the thyroid or thymus, then marked inhibition occurs. Removal of one gland from one system and of either the thyroid or the thymus results in practically no inhibition. If both glands be removed from each system, then, in order to induce inhibition, both of the intermediate glands must also be removed. From this it would appear that there are two systems which control the reaction and that these systems are connected through two apparently interchangeable glands, the thyroid and the thymus.—J. F.

ENDOCRINE organs in experimental gas gangrene (Les organes a sécrétion interne dans la gangréne gazeuse experimentale). Van Geheuchten (P.), Ann. de l'inst. Pasteur (Paris), 1921, **35,** 396-419.

After giving a comprehensive review of the literature dealing with the effect of gas gangrene on the endocrine organs the author proceeds to describe the results of his own experiments on 65 guinea pigs treated with various types of gas producing bacilli. The results of his study indicate that the modifications of the glands of internal secretion in the infections caused by the anerobic micro-organisms are entirely comparable to those observed in infections and intoxications of very diverse origin. They are of slight degree in the **thyroid** and the **hypophysis** and severe in the **adrenal** capsule margins. In the latter the lesions are characterized by a discharge of the lipoid

material of the spongiosa into the blood, and almost all the cholesterin is lost within about 48 hours. The neutral fats disappear somewhat less rapidly. They persist and even increase in the glomerulae and neighboring cells.—F. S. H.

Case of GIGANTISM (Geval van reuzengroei). Hekman (J. J.), Nederl. Tijdschr. v. Geneesk. (Haarlem), 1921, **65** (II), 1498.

Demonstration of a tall girl of 19 (190 cm.). Hands, arms, feet and legs were very long. There were axillary and pubic hairs. Menstruation began at 17 and has been normal. No changes in the sella or in the eyes were noted. The bone formation was retarded as shown by radioscopy. There was a slight prognathism. Blood sugar on the empty stomach was 0.14%; after 100 gm. glucose was 0.24%. The most probable diagnosis is dysfunction of the **hypophysis** with a secondary insufficiency of the **ovaries**.—J. K.

(GONADS) A case of hermaphroditism (Ein Fall von Hermaphroditismus). Beneke, München. med. Wchnschr., 1921, **68,** 1064.

Under the long clitoris ended a hypospadial urethea, which led to the vagina and the small uterus. Instead of the ovaries there was on the right side a very small organ with a few paradidymis canals and on the left side an organ the size of a pea with small seminal canals.—J. K.

(GONADS) Steinach's theory of a puberty-gland (Zur Lehre Steinachs von der Pubertätsdrüse). Dietrich (A.), Deutsche med. Wchnschr, (Berlin), 1921, **47,** 1080; München. med. Wchnschr., 1921, **68,** 1034-1035.

The interstitial cells of the testicles have a nutritive role; they play an important part in the resorption of substances formed in the other cells. Neither in the **testicle** or **ovary** has an independent function of the interstitial cells been proved.—J. K.

(GONADS) Steinach's operation (Die Steinachsche Methode). Klein, Berlin klin. Wchnschr., 1921, **58,** 1087; Wiener klin. Wchnschr., 1921, **34,** 518.

Indications for the transplantation of testicles are deficiency symptoms after castration, eunuchoidism, and homosexuality. In this last case a testicle must first be removed. Testicles of animals are perhaps useful. For the ligation of the vas deferens precocious senility is the most important indication. In cases of hyperfunction of one testicle, ligation of the corresponding vas deferens is perhaps useful.—J. K.

(GONADS) Carbohydrate content of the King salmon tissues during the spawning migration. Greene (C. W.), J. Biol. Chem. (Balt.), 1921, **48,** 429-436.

The ovaries of the series of 6 fish are remarkably uniform in glucose content whatever the stages of the journey to spawning. The percentages are from 0.08 to 0.18. The analysis of one lot of eggs free from ovarian tissue gave 0.09% glucose. This is near the average for the ovary of the series of immature fish. It demonstrates that the carbohydrate content in this growing tissue is independent of the stage of development and the duration of the fast. No glucose was found in the testes of nearly mature salmon.

—F. S. H.

Function of the GONADS and psychical disturbances (Keimdrüsenfunktion und Seelenstörung). Kretschmer (E.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 649-650.

The author points out the importance of the endocrine functions of the sexual glands in psychical diseases as is proven by the sexual symptoms of patients with such disturbances and the psychical symptoms as seen in diseases of the sexual organs.—J. K.

(GONADS) Steinach's operation in sexual impotency (Steinachsche Operation in der Behandlung der Impotenz). Littaur, Deutsche med. Wchnschr. (Berlin), 1921, **47**, 1248.

Littaur has seen good effects from this treatment. The only proof that is given is that—the patients wrote him very grateful letters!—J. K.

(GONADS) A criticism of Steinach's rejuvenation operation (Zur Beurteilung der Steinachschen Verjüngungsoperation). Mendel (K.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 986-989.

A healthy man with precocious senility was operated upon by ligation of the vas deferens. Immediately after the operation a psychosis developed with serious sexual irritability and sexual hallucinations. Death followed. The author warns against this treatment. It has not been proved that Steinach's "Pubertätsdrüse" exists. It has not been proved that ligation of the vas deferens between the epididymis and testis causes a rejuvenation of the interstitial cells. Experiments on rats cannot be compared to clinical work in man. Steinach's operation is not without danger as is proved by the case cited. Transplantation of testicles may be considered as at least a more logical operation than ligation of the vas deferens.—J. K.

(GONADS) Steinach's rejuvenation operation (Die Steinachsche Verjüngungsoperation). Mendel (K.), Berl. klin. Wchnschr., 1921, **58**, 1011.

Data have been reported in the Deutsche med. Wchnschr.—J. K.

A chemical fact in the study of the GONADS (Contributi chimici allo studis delle ghiandole genitali). Russo (G.), Gazz. d. Osp. (Milano), 1921, **42**, 735.

In some animals the testicles contain much more nitrogen when active than when at rest. In the ovaries this difference is much smaller.—J. K.

(GONADS) Clinical influence of ligation of the vas deferens (Die klinische Wirkungen der Vasoligatur). Schmidt (P.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 1248.

The author has carried out Steinach's operation in 20 cases. The effect on the sexual disturbances is splendid. (As no details are given, it is impossible to evaluate this statement).—J. K.

(GONADS) Formation of a hymen in the urethra (Ueber Hymenbildung in der Harnröhre). Schmincke, Berlin klin. Wchnschr., 1921, **58**, 1020.

A man of 22 died of a sarcoma of the neck. At the autopsy there was found cryptorchism, with absence of beard and pubic hair. In the pars prostatica of the urethra was a hymen which closed the entrance of the vagina masculina. The diagnosis was pseudo-hermaphroditismus musculinus internus.—J. K.

HYPERNEPHROMA. Gagstetter, Deutsche med. Wchnschr. (Berlin), 1921, **47**, 1150.

Of no endocrine interest.—J. K.

HYPERTENSION (Kurzen Beitrag zur Frage der Hypertonia). Fahr (T.), Berl. klin. Wchnschr., 1921, **58**, 730-731.

Most authors believe that in arteriosclerotic hypertension the sclerosis of the blood vessels is caused by the high blood-pressure. Fahr, however, has always believed that sclerosis (especially of the vessels of the kidney) occurs first, and later, a rise of blood pressure. In 1910 Neubauer stated that in hypertension there is always hyperglycemia. Many authors did not find this, but now Neubauer's views have been entirely confirmed by Hitzenberg and Richter Quittner (Wiener Arch. f. inn. Med., 1921, **2**, 189). These authors believe that there is an increase of **adrenalin** in the blood and that this causes both the increased blood sugar and the rise of the blood pressure. Fahr states that the increased amount of blood sugar may be due to a primary sclerosis of the vessels of the **pancreas.** It is well known that the vessels of this organ often show arteriosclerotic changes. He believes that this is followed by the secretion of a diminished quantity of hormone and that this causes the hyperglycemia. On the other hand, there is an antagonism between the pancreas and chromaphil tissue. Thus the high blood pressure as

well as the hyperglycemia may also be due partly to an increased secretion of adrenalin. (The article is full of unproved statements.)
—J. K.

(HYPOPHYSIS) Hypopituitarism after cerebral influenza (Hypopituitarismus nach Gehirn-Grippe). Fendel, Deutsche med. Wchnschr. (Berlin), 1921, **47**, 991.

A boy of 13 became very fat following an attack of influenza. A skiagram of the sella turcica was not made. There was no genital atrophy, no symptoms of brain tumor nor hemianopsia. The intelligence was normal. (The abstractor is not able to understand why this is regarded as a case of hypopituitarism.)—J. K.

Diagnosis of HYPOPHYSIS insufficiency (Diagnose van der hypophysenzwakte). Fliess (W.), Med. Weekblad (Haarlem), 1921, **28**, 309-315.

A translation of an article from the Med. Klinik.—J. K.

(HYPOPHYSIS) A case of acromegalic giantism (Sobre um caso de giantismo acromegalico). Flores (N.) & Diaz (A.), Revista dos Cursos (Porto Alegre), 1921, **7**, 159-174.

The case is that of a typical acromegalic giant 2.16 m. tall with a reach of 2.31 m. He was only slightly active sexually, and had moderately developed external genitalia. There was a slight degree of kyphosis. There was no glycosuria; glycemia was 0.136; acidity of urine was 0.00052; creatinin, 0.0013; blood cholesterin, 0.633. There was chronic choked disc of the right eye. The sella turcica was enlarged.—B. A. H.

The PITUITARY gland in children. Fraser (J.), Edinb. M. J., 1921, **27**, 136-144.

This study is based upon a series of forty pituitary glands obtained from children between the ages of one year and twelve years. Comparing the pituitary of the child with that of the adult it is found that the variation in the size of the "pituitary lake" (intra-glandular cleft, Koelliker's space, the remains of the original cavity of Rathke's pouch) is apparently a feature distinctive to the child, or at least to the period between birth and adolescence. The author holds that in children the pituitary exhibits distinct periods of activity and rest. There seems to be a distinct relation between the stage of activity of the pars intermedia and the amount of distention of the pituitary lake. While the pars intermedia is in a resting state the lake is small, and in certain cases practically empty. As the pars intermedia becomes more active, secretion begins to accumulate within the lake until it becomes distended to a considerable degree. The pars intermedia then returns to its resting state,

and the lake gradually returns to a slit-like space. The author believes that the major part of the contents of the lake is a homogeneous colloid material derived from the pars intermedia; there is also a secondary contribution from the eosinophil cells of the anterior lobe. There is found to be an active stage of the anterior lobe which is synchronous with the active stage of the pars intermedia, and is partly preliminary and partly synchronous with the distention of the pituitary lake. The changes of stage noted are the same in the two sexes. They have no relationship to any morbid condition.—W. J. A.

(THYROID) Suggestions regarding the role of the HYPOPHYSIS in Graves' disease and myxedema. Friedman (G. A.), N. York M. J. (New York), 1921, **113**, 370-374.

The hypophysis appears to show histological changes in Graves' disease similar to those of hyperpituitarism and in myxedema to those of hypopituitarism. Therefore, there is a certain degree of hypophyseal involvement in conditions of disturbed thyroid function. Chromophilia of the anterior lobe is characteristic for Graves' disease: chromophobia for myxedema. The following symptoms and signs of Graves' disease may in part be attributed to hypophyseal overactivity: increased metabolic rate (emaciation), tendency to glycosuria, insomnia and irritability, intestinal spasticity, tendency to miscarriage, and acceleration of epiphyseal closure. The symptoms and signs of myxedema attributable to hypophyseal underactivity are as follows: decreased metabolic rate (adiposity), high sugar tolerance, mental depression, intestinal atony, rarity of miscarriage, and retardation of epiphyseal closure. Pituitary products should be contraindicated in the treatment of exophthalmic goiter patients and indicated in addition to thyroid in myxedematous subjects.—H. W.

(HYPOPHYSIS) Adiposogenital syndrome in adults (Contribution à l'étude du syndrome adiposo-génital d'origine hypophysaire chez l'adulte). Goudal (J. M.), Thèse de Paris, 1919, 72 p., No. 250.

According to Goudal the adiposogenital syndrome in the adult is characterized by: (1) rapid and progressive obesity; (2) atrophy of the genital organs and disappearance of the sexual functions, constituting late **infantilism**; (3) association of cerebral and visual disturbances. This triad of symptoms is sometimes accompanied by slight signs of **acromegaly** and frequently by **diabetes insipidus.** The diagnosis of the condition rests on the presence of the ocular signs, especially bitemporal hemianopsia, so that the patients are frequently sent to the physician by the oculist who finds other signs of the syndrome present.—Med. Sc. Abst. & Rev., 1920, **2**, 134.

(HYPOPHYSIS) Defects of membranous bones, exophthalmos and polyuria in childhood: Is it dyspituitarism? Hand (A.), Am. J. M. Sc. (Phila.), 1921, **162**, 509-515.

The author has in times past reported cases of children presenting this triad of symptoms as associated with tuberculosis. He brings forward his own cases again and discusses them in the light of similar studies by others together with a new case and the review of theories which have been advanced. He concludes that further data are needed for a satisfactory explanation.—J. F.

(HYPOPHYSIS) Dyspituitarism so-called: absorption of membranous bones, exophthalmos and polyuria. Report of two cases. Hand (A.), Tr. Am. Pediat. Soc., 1920, **32**, 154.

Hand reviews the literature on this peculiar condition. Six cases have been reported by Christian, Schiller (2), Kay, and himself. He goes into detail in his own cases. A boy three years of age had had great thirst and polyuria for 8 weeks. He was undersized, and had bronzed skin. There was exophthalmos. The thyroid was not enlarged. There was abdominal distention with an enlarged liver and spleen and umbilical hernia. The skin over the abdomen presented eczema and petechial eruption. The urine was sugar-free, but showed some albumin. He ran an irregular temperature from 99° to 105°, which reacted somewhat to quinine. Broncho-pneumonia set in later, but a diagnosis of tuberculosis was made because of the general course of the disease. The boy died suddenly. At the post-mortem examination, as the scalp was stripped off, a yellow spot about 2 cm. in diameter was noticed extending through the entire thickness of the skull; it was soft and movable. Other small areas which did not extend through the vault were seen on the outer surface. These were thought to be tubercular.

The second was a boy of four years. At the age of two, a tumor-like mass had been removed from the left parietal region. There was an absence of bone beneath it down to the dura. There was no evidence of its being a gumma or a sarcoma. There was a slight degree of inflammation, mainly myxedematous. Since then exophthalmos had developed, but no polyuria. The radiogram of the skull showed bone changes, but no changes in the sella.

Hand objects to the theory of hypopituitary etiology on the following grounds: Two of the six reported cases have not shown polyuria. In two having polyuria and probably in all four, exophthalmos and bone changes came first. Injection of pituitary extract, although diminishing the polyuria, had no effect on the bone changes. The exophthalmos is probably not of toxic or endocrinic origin, but mechanical, due to involvement of the orbital plate of the frontal bone as shown by the four who have been studied by the x-ray. The bone changes are not such as would be produced by

a chemical substance, which ought to effect the bones in their entirety. Polyuria probably depends upon disturbed function of the hypophysis, due to pressure. Other possible theories are that the bone changes are those of osteosarcoma. A chronic infective process may also be considered, since two of the cases started with decay of the teeth and two had a history of a discharging ear.—M. B. G.

The importance of HYPOPHYSEAL lesions in diabetes insipidus (Über die Bedeutung der Hypophysenveränderungen bei Diabetes insipidus). v. Hann (F.), Frankf. Ztschr. f. Path. (Weisb.), 1918, **21**, 337-336.

V. Hann reports three cases with autopsy findings and reviews the literature of seventeen other cases with post-mortem findings. He concludes that every case is associated with a "dysfunction" of the hypophysis. Hypophyseal lesions are found in diabetes insipidus only when for some cause, as a tumor or inflammatory reaction, the posterior lobe is destroyed or severely injured while the anterior lobe remains functionally intact. The onset of diabetes insipidus is dependent upon a functionally intact heart and renal system in addition to the functional disturbance of the neurohypophysis. He found no evidence of associated **thyroid** disease in the cases reported.
—D. M.

Experiences with the extract of HYPOPHYSIS in labour (Unsere Erfahrungen mit dem Hypophysen-extrakt Physormon als Wehenmittel). Hellmuth (K.), Centralbl. f. Gyn. (Leipzig), 1921, **45**, 1320-1324.

This preparation is warmly recommended for obstetrical purposes. It is an alcohol-chloroform extract from fresh hypophyses (pars posterior and intermedia) of cows.—J. K.

Action of HYPOPHYSIS extract in cerebral polyuria (Acción del extracto de hipofisis sobre la poliuria cerebral). Houssay (B. A.) & Hug (E.), Rev. Asoc. méd. argent. (Buenos Aires), 1921, **34**, 443.

It is necessary to distinguish the immediate action and that over a period of 24 hours in studying hypophysis extract. In the normal dog or in one having polyuria there is always an immediate increase in diuresis. Polyuria was produced by ablation of the hypophysis or by piqûre in the para-infundibular region.—B. A. H.

Tumor of HYPOPHYSIS successfully removed (Glücklich operierter Hypophysentumor). Kirschner, Deutsche med. Wchnschr. (Berlin, 1921, **47**, 879-880 (Berl. klin. Wchnschr., 1921, **58**, 976-977).

The patient had diminuition of the visual field and decreased vision. The endonasal removal of an angiosarcoma of the hypophy-

sis was followed by marked improvement. The visual field became nearly normal again.—J. K.

Assay of HYPOPHYSEAL preparations and other materials used in labor (Zur Wertbestimmung der Hypophysenpräparate und anderer Wehenmittel). Kochmann (M.), Ztschr. f. physiol. Chem. (Berl. u. Leipz.), 1921, **115**, 305-310.

This method based on the contraction of the uterine segment does not differ in any essential particular from those already found in the literature with the possible exception that the rhythmical contractions of the uterus are inhibited by suspending the segment in a Ca-poor Ringer's solution to which $MgCl_2$ has been added.

—F. S. H.

The opinion of the clinic in Utrecht about the use of PITUITRIN (Het standpunkt der Utrechtsche Klinick ten opzichte van het gebruck von pituitrine). Kouwer (B. J.), Vox Medicorum (Utrecht), 1921, **21**, 129-131.

The author is the director of the University Clinic for obstetrics in Utrecht. The first essential in obstetrical practice, he believes, is patience. He thinks that if students are taught to use pituitrin they will abuse it when they enter practice. It is not easy to give a satisfactory indication for the use of pituitrin. In 20,000 childbirths the author reports that pituitrin was given 15 or 20 times. In many of these cases the injections produced no results.—J. K.

(HYPOPHYSIS) Report on the regulation of the use of bichloride of mercury and pituitrin by mid-wives (Rapport sur la réglementation de l'emploi par les sages femmes du sublimé et de la pituitrine). Le Lorier, Bull. soc. obst. et. gyn. d. Par., 1921, **10**, 312-320.

Hypophyseal preparations of any type should be considered as dangerous drugs and their use should be forbidden to mid-wives.

—F. S. H.

Diabète insipide et HYPOPHYSE. Lereboullet (P.), Progress méd. (Par.), 1919, 3.s. **34**, 363-366.

Lereboullet in the course of his regular lecture on this subject describes the case of a man of 50 who had had syphilis at 18 and at 31 protracted pneumonia, after which there was retrogressive infantilism, impotence, asthenia, falling of the hair and tendency to obesity. There was also polyuria. Treatment of various kinds proved futile until pituitary treatment was given, and then the output of urine dropped from the 7 or 8 liters, which had been the average for ten years, to the normal figure as long as the pituitary

treatment was kept up. The extract from the posterior lobe alone was most effectual.—J. Am. M. Ass., **73**, 1731.

Opothérapie HYPOPHYSAIRE et diabete insipide. Lereboullet (P.), Paris méd., 1919, **9**, 353-357.

Lereboullet alludes to a case of diabetes insipidus reported by him five years ago in which the symptoms were temporarily relieved by subcutaneous injection of the posterior lobe of the hypophysis. Since then many other similar cases have been published showing that diabetes insipidus is often the direct or indirect manifestation of a change in the hypophysis which can be benefited by such treatment. Its action, however, is only transitory and rarely lasts more than twenty-four hours. The treatment therefore does not modify to any extent the prognosis of diabetes insipidus. It cannot remove the causal lesion or render etiological treatment unnecessary, e. g., when the condition is due to inherited or acquired syphilis. It does not prevent a subsequent operation which is always serious and often fatal. But its value lies in causing a temporary relief of the patient's symptoms. It dispels the intense thirst for a few hours, calms the nervous symptoms, and restores sleep. The treatment is quite harmless, so that daily injections of 1-2 cc. of the extract of the posterior lobe may be continued for a long period, and will be found to have a favorable action not only on the diuresis and thirst, but also on the obesity, general condition, development of the genital system, and even on growth.—Med. Sc. Abst. & Rev.

(HYPOPHYSIS) Action vasculaire comparée de l'histamine et de l'extrait d'hypophyse associes à l'adrénaline. Llosa (J. B.), Compt. rend. Soc. de biol. (Par.), 1920, **83**, 1358.

See Endocrin., **5**, 362.

The question of PITUITRIN (Het pituitrinevraagstuk). Mendels (W. A.), Vox Medicorum (Utrecht), 1921, **21**, 154-155.

Mendels states that in 1,000 injections of pituitrin in childbirth he has never observed any undesirable results. It is a valuable drug, especially in multiparae. As even the smallest trace of alcohol destroys the activity of pituitrin, the syringe should not be cleaned with it. He recommends an American preparation, and mentions several German and Dutch preparations of pituitrin as inactive and useless. [The opinion that alcohol injures pituitrin has not been sustained by careful American investigation.—Ed.]—J. K.

Extirpation of HYPOPHYSIS. Oehlecker, Berlin. klin. Wchnschr., 1921, **58**, 821.

In case of a patient with acromegaly and another with dystrophia adiposogenitalis, Oehlecker removed the hypophysis by a

modification of Schloffer's operation with good result. In 3 other cases in which other tumors pressed on the hypophysis the operation failed to prevent a fatal termination, though in one case it was followed by a marked remission of the symptoms.—J. K.

HYPOPHYSIS extract as a heart tonic (Zur Verwendung von Hypophysenextrakt als Herztonikum). Pohl (A.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 1162.

A patient, with cancer of the breast, who had a very weak pulse was greatly benefited by pituitrin injections. Injections of camphor and caffein were without effect. Pituitrin did not work so well in other cases. In a hysterical girl complaints of "weakness" ceased when pituglandol was regularly administered.—J. K.

Roentgen therapy in two cases of HYPOPHYSEAL dystrophia adiposogenitalis (Zwei Fälle von hypophysärer Dystrophia adiposogenitalis und ihre Behandlung mittels Röntgenbestrahlung). Rauschburg (P.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 1291-1292.

I. A man of 19 presented severe headaches, giddiness, vomiting, typical eye symptoms (papillitis); a skiagram of the sella showed that the anterior clinoid processes were shorter than normal and that the dorsum sellae had disappeared. Loss of libido sexualis, small thyroid and loss of hair were also features. X-ray treatment resulted successfully. First the headaches and vomiting disappeared; the vision became much better and the hairs began to grow again. Hypophysis tablets were then given at the same time. The patient was able to begin his work again.

II. A woman of 50 had adiposity, papillitis of both eyes, and headaches. On the skiagram the sella showed somewhat deeper than normal. Though she was blind, in this case x-ray treatment resulted in brilliant success. The vision became 5/10 in both eyes—J. K.

Tumor of HYPOPHYSIS. Schloffer, Wiener klin. Wchnschr., 1921, **34**, 518.

Demonstration of a patient in whom a malignant adenoma of the hypophysis had been removed by the endonasal route. Slight improvement of the eye symptoms followed. No other details are given.—J. K.

Cyst of the duct of the HYPOPHYSIS (Hypophysengangzyste). Schuster, Berl. klin. Wchnschr., 1921, **58**, 682.

A patient showed atrophy of the optic nerve. No symptoms of acromegaly or dystrophia adiposogenitalis were found. Radioscopy showed a small sella turcica. At post-mortem a cyst of the duct of the hypophysis was found.—J. K.

MIGRAINE, its cause and treatment. Wolfe (S.), Northwest Med. (Seattle) 1921, **20**, 288-291.

The author considers an endocrine fault as a possible basis for migraine, but can not yet indict any one of the internal secretions specifically. Our knowledge of endocrinology is still so vague, that neither in the etiology nor in the therapy of migraine, can we do more than grope, when we attempt explanations or relief. **Pituitary** headaches are recognized but not considered true migraine. Migraine usually appears at about the time of puberty and is prone to disappear in women at the climacteric and in men about the same age.
—H. L.

PITUITARY standardization. Tate (G.), Pharm. J., 1921, (4) **52**, 268-269.

The difficulties met in selecting a standard are cited. Different lots of U.S.P. histamine standard may vary in activity. Histamine is depressant to the rat uterus, while infundibular extract is stimulant. Autolytic and bacterial changes in the slaughter houses might be detected by the use of a standard with the same action on the rat uterus as infundibular extract. In the excised uterus test on the virgin guinea pig, it was found that the results are changed by variations in the proportions of K and Ca in the Locke solution used; regular increases in the contractions were obtained by increasing the amount of KCl. Infundibular extracts deteriorate too quickly in the tropics to be employed as standards; samples sent out in March, 1920, and in September, 1920, had deteriorated to the same extent (30%) by February, 1921. The remaining activity was shown by tests on the rat uterus to be due to pituitrin and not to histamine. The amount of 1.5% KCl solution which had to be added to 60 cc. Locke solution to produce a submaximal contraction of a portion of excised virgin guinea pig uterus was found to be 10 times the amount of 1:200 infundibular solution required to produce the same effect. The ratio is the same with different uteri, although different amounts can be used. The same amount of KCl is required to produce equal contractions whether in 1.5% or 15% solutions. The latter is more convenient, as the amounts are the same as the amount of infundibular extract solution to produce the same results. If more of the extract solution than of 15% KCl solution is required to produce the same submaximal contraction, then the extract is below standard. The same applies to the excised uterus of the virgin rat. An excess of $CaCl_2$ in the Locke's solution antagonizes the KCl. The contraction produced by KCl has slightly less lifting power than that due to infundibular extract.—Chem. Abst., **15**, 2336.

PITUITRIN. Van den Bergh, Vox Medicorum (Utrecht), 1921, **21**, 153-154.

When pituitrin is given where there is a strict indication, it is a splendid obstetric aid.—J. K.

Intermediate processes in DIABETES INSIPIDUS and their significance (Ueber intermediäre Vorgänge beim Diabetes insipidus und ihre Bedeutung für die Kenntniss vom Wesen dieses Leidens). Veil (W.), Biochem. Ztschr. (Berl.), 1918, **91**, 317-389.

Diabetes insipidus is an individual disease characterized by the symptom complex of polyuria, polydipsia, low concentration of urine and changes in the intermediary water and salt relations. The lowered concentration of the urine is to be recognized as a practical symptom of variable value. The studies were carried out on patients having the disorder. According to the type of metabolic disturbance observed it appears as if there are two fundamentally different diseases which can be classed as hyper-osmotic and hypo-osmotic diabetes insipidus. In the former the ability of the organism to retain its water is lost. In the latter the whole organism is on another lower osmotic level. Studies of the intermediary exchanges of salt and water showed that the trouble is not renal, but principally due to tissue anomalies. The kind of relation supposed to exist between the nervous system and the internal secretions on the one hand and diabetes insipidus on the other is completely unknown. The extracts of the posterior lobe of the hypophysis are by no means specific in their action.—F. S. H.

The HYPOPHYSIS in the pathogenesis of diabetes (Ueber die Bedeutung der Hypophyse in der Pathogenese des Diabetes mellitus). Verron (O.), Zentralbl. f. allg. Path. u. path. Anat. (Jena), 1921, **31**, 521-531.

Description of 6 cases of diabetes with exact post-mortem reports.

1. Atrophy of the pancreas; goiter; both lobes of the hypophysis enlarged; in the pars glandularis a largely increased number of eosinophil cells were found. The pars intermedia was normal, but with large vacuoles. The pars nervosa was normal.

2. The pancreas was normal; there were no changes in the islands of Langerhans. The hypophysis was small, without changes, except hyperemia of the pars anterior.

3. The pancreas showed anteriosclerosis and contained much fat. The islets were absolutely normal. In the hypophysis the pars intermedia was very small. The pars nervosa was normal, but contained may basophil cells. In the pars anterior were seen many mitoses.

4. The pancreas showed only unimportant sclerosis in some islets. In the hypophysis the pars anterior was small, the lobus posterior large. In the pars anterior a large number of eosinophil

cells and in the pars posterior, pigmentation was seen. The pars intermedia showed necrosis.

5. The pancreas was slightly atrophic. There were psammoma in the pars intermedia of the hypophysis.

6. Metastasis of a cancer was found in the hypophysis. The pars posterior and intermedia had been destroyed by the tumor.

The author believes that these cases prove the existence of hypophyseal diabetes. (He seems to be quite unaware of the evidence that changes in the hypophysis have no influence on metabolism and that changes in metabolism are due to pressure on the midbrain.)

—J. K.

HYPOPHYSEAL adiposity with psychic disturbance (Hypophysäre Adiposität mit psychischer Störung). Weggandt, Deutsche med. Wchnschr. (Berlin), 1921, **47**, 881.

Data reported elsewhere.—J. K.

(HYPOPHYSIS) Changes in the cartilages of the larnyx in acromegaly (Veränderungen des knorpeligen Kehlkopfgerüstes bei Akromegalie). Weingärtner, Deutsche med. Wchnschr. (Berlin), 1921, **47**, 1111.

In man complete ossification of the thyroid cartilage of the larnyx is normal. In woman it is seen in cases of acromegaly with tumors of the hypophysis, but not in acromegaly without tumors in the hypophysis.—J. K.

Tumors of HYPOPHYSIS with special reference to symptoms (Contributio alla conoscenza dei tumori dell' ipofisi con praticolare riguardo alla loro sintomatologia). Zino (A.), Gaz. d. Osped. (Milano), 1921, **42**, 740-743.

Description of three cases with the ordinary symptoms of headache, giddiness, loss of vision and changes in the sella turcica.—J. K.

INFANTILISM in children. Leebron (J. D.), Penn. M. J. (Harrisburg), 1921, **24**, 810-812.

The classification of Gilford is referred to, and then a brief description follows of ateliosis and progeria, in which the etiology is unknown except that the cases are familial and hereditary. The symptomatic group includes: Herter's intestinal infantilism; Bromwell's pancreatic infantilism; the Lorrain type; the Brissaud variety; the Fröelich syndrome. The last three are probably due to insufficient **thyroid** or **pituitary** secretion. Finally come the retarded development and growth associated with congenital heart disease; malnutrition from tuberculosis; arterial hypoplasia; lymphatic diathesis; congenital lues. The importance of radiograms of the hand in diagnosing delayed ossification is emphasized. Thyroid extract, according to Leebron, is often helpful.—H. L.

A case of INFANTILISM with enuresis (Ein Fall von Infantilismus mit Enuresis). Trömner, Deutsche med. Wchnschr. (Berlin), 1921, **47**, 1179.

A girl of 16 weighed 28 kilograms, with a height of 135 cm. There was no hair on the pubes or in the axillae, and menstruation was absent. The diagnosis was polyglandular infantilism. This patient suffered also with enuresis and had a slight spina bifida. —J. K.

Calcium metabolism and INTERNAL SECRETIONS (Kalkstoffwechsel und innere Sekretion). Bauer (J.), Wien. klin. Wchnschr., 1921, **34**, 314-315.

A general review without new data.—J. K.

Antithrombin an INTERNAL SECRETION of nuclear origin (Méchanisme régulateur de la fluidité du sang. Existence d' une sécrétion interne d'origine nucléaire). Doyon (M.), Médicine (Paris), 1921, **2**, 918-922..

One of the factors in the maintenance of fluidity of circulating blood is an internal secretion known under the name of antithrombine. This substance is a nucleoproteid active in vitro. Its origin is in the cellular nucleus. All the nuclear acids exercise an anticoagulant action in vitro. Their use allows of obtaining a stable plasma resisting the action of serum. In cats and dogs it is only the liver which appears to contain any antithrombine easily mobilisable, but it is possible that all organs because of their cellular nuclei are the starting point of the internal anti-coagulant secretion.—R. G. H.

(INTERNAL SECRETIONS) Secrezioni interne e sistema nervosa. Laignel-Lavastine, Arch. gen. di neurol. psich. e psicolanal. (Napoli), 1921, **2**, 5-52.

Republication in Italian of material reviewed in Endocrinology, 1919, **4**, 342. —R. G. H.

(LIPOID GLANDS) On glandular adipose tissue, and its relation to other endocrine organs and to the vitamine problem. Cramer (W.), Brit. J. Exper. Path. (Lond.), 1921, **1**, 184.

While in most animals the naked eye appearance of body fat from different sites of the body is fairly uniform, in certain species of animals, as, for example, the white rat and the tame mouse, two distinct types of adipose tissue can be recognized: (1) the ordinary yellowish-white fat; (2) reddish-brown masses. The three most important masses of the second type occur: (a) between the scapulae with extensions between the muscles; (b) in the thorax in front of the vertebral column along the thoracic aorta; (c) in the abdomen between the kidneys along the aorta, extending upward enclosing

the suprarenal glands and downward enclosing, in the female, the ovaries. These fatty organs differ from ordinary adipose tissue in being rich in "lipoids," especially cholesterol and its compounds, and in having a very rich blood supply. Cramer suggests that these lipoid-rich fatty organs be designated "lipoid glands" or "cholesterin glands." Reasoning by analogy, he further suggests a relationship between these lipoid glands and the **suprarenal** cortex. He has made some observations which suggest that these lipoid glands are concerned in the problem of **vitamines** and deficiency diseases.
—D. M.

Contribution to the study of cerebral metabolism by the method of partial circulation. IV. Internal secretion of the LIVER and morphological variations of the cerebral neurones. Renauld-Capart (H.), Arch. intern. de physiol. (Paris), 1921, **16**, 119-161.

It is concluded that it is necessary for the blood to circulate through the liver if cerebral activity is to continue. It is suggested that the liver affords this facilitation either through a detoxicating process or because of the elaboration of a specific **internal secretion.** The latter hypothesis is supported by the evidence. Moreover, when hepatic function is arrested there is produced in the cerebral neurones a condition of chromatolysis, which is succeeded by a chromatophile regeneration corresponding with the return of function of the centers when the blood supplying the brain is allowed to pass through the liver. The statement is made: "Cerebral metabolism in its entirety, psychic effort and conscious perception, are directly dependent on an internal secretion of the liver, elaborated as a thermolabile substance, the action of which seems to facilitate the continuous formation of the chromatophile substance of the neurones."—Chem. Abst., **15**, 2115.

(MENOPAUSE) The prognosis in high blood pressure. Graham-Stewart (A.), Practitioner (London), 1921, **107**, 183-200.

The author briefly refers to the high blood pressure often encountered in women at or near the menopause. Of all types, he considers this group most amenable to treatment. "The underlying pathology is probably an endocrine disturbance, associated with emotional states and a hypersensitivity of the nervous and vasomotor systems."—H. L.

A case of MYOTONIA DYSTROPHICA (Ein Fall von myotonischer Dystrophie). Full, München. med. Wchnschr., 1921, **68**, 1064.

A man of 46 had dystrophy of the muscles of hands, forearms and of the sterno-cleidomastoidei, together with facies myopathica. Hypoplasia of the **thyroid** was noted. Probably the endocrine disturbance as well as the myotonia are both due to changes in the involuntary nervous system.—J. K.

(ORGANOTHERAPY) Treatment of sterility by means of organic extracts. Bercovitch (A.), Med. Rec. (New York), 1921, **99**, 1052-1055.

A first essential is to be reasonably sure that the sterility in a given case has an endocrine origin; second, to recognize the ductless gland chiefly responsible, and whether it is secreting too much or too little. The close functional correlation of **thyroid**, anterior **pituitary** and **ovaries** is emphasized. The pituitary type originating prior to or after adolescence and the preadolescent hypothyroid and ovarian types are briefly described. Then follows brief records of nine patients, illustrative of the above types, all women, suffering from partial or complete amenorrhoea, with or without obesity, or dysmenorrhoea. Depending on the organ chiefly at fault they were given thyroid extract, or pituitary anterior lobe, or ovarian extract. No pluriglandular preparations were administered. **Menstruation** returned, or was normally regulated in all of them, and pregnancy followed each case, though most of them had been married and sterile for many years. (The author is to be congratulated on his remarkable success. Since many others have been by no means as fortunate in their results, one is tempted to inquire how many cases were unsuccessfully treated, so that the percentage of cure could be ascertained.)—H. L.

(ORGANOTHERAPY) The treatment of the chronic intestinal invalid. Bryant (J.), Am. J. M. Sc. (Phila.), 1921, **161**, 74.

In discussing the hyposthenic variety of subjects with gastrointestinal manifestations, Bryant devotes a page to glandular therapy. Whole gland **suprarenal** preparation in five grain doses is used in certain cases of chronic exhaustion. Bryant is convinced that in these cases better results are obtained with than without this preparation. In many instances, he also finds one-tenth and one-fourth grain doses of **thyroid** useful. In women **ovarian** preparations are certainly of value in selected cases.—J. F.

(ORGANOTHERAPY) A psychological study of some mental defects in the normal dull adolescent. Clark (L. P.), Med. Rec. (New York), 1921, **99**, 991-996.

A sentence is devoted as follows to the ductless gland aspect: "While there are still chances for a wider and more exact extension of endocrinology in mental defects, as yet it has not materially altered the general statement that once a definite determination of any degree of feeblemindedness has been made in a child, the condition which remains is hopeless so far as recovery or cure is concerned."—H. L.

Concerning the result of the active factor in ORGANOTHERAPY for menstrual disorders (Ueber die Erfolge und das wirksame

Prinzip der Organextrakttherapie bei Menstruationsstörungen). Esch (P.), Zentralbl. f. Gynak. (Leipzic), 1920, **44**, 561-568.

Esch calls attention to the apparently paradoxical results so often observed with organotherapy. In the case of the ovary, for example, he refers to the good results reported by various authors from the administration of **ovarian** or **corpus luteum** extract in cases of hyperfunction of the ovary, especially the functional hemorrhages of puberty and those of later life. On the other hand, the same preparations are reported to give satisfactory results in cases of hypofunction, as in **amenorrhea.** He brings out similar paradoxes with **pituitary** therapy. His explanation of these matters is that we are not dealing in organotherapy with specific secretions, but that the results are due to factors of non-specific nature. He is impressed with the work of Köhler, who obtained, with Enteroglandol, an extract of the intestinal mucosa, results in the treatment of amenorrhea which were similar to those following the use of luteoglandol, a corpus luteum preparation. Biedl has also observed the similarity of toxic symptoms produced by various organ extracts with those of peptone poisoning. Esch has treated a number of cases of menstrual disorder, especially **menorrhagia,** by the parenteral (intramuscular) administration of protein bodies, such as breast milk. These observations support his hypothesis that the action of the organ extracts is of a non-specific protein nature.—E. N.

Carcinomatous dermoid cysts of the OVARY (Karzinomatöse Dermoidzyzten des Ovariums). Eisenstädter (D.), Monats. f. Geburtsh. u. Gynäk. (Berlin), 1921, **54**, 360-366.

Not of endocrine nature.—F. S. H.

The specific secretion of the OVARY (Ueber das specifische Ovarialsekret). Fellner (O. O.), Zentralbl. f. Gynäk. (Leipsic), 1920, **44**, 1133-1138.

This article is a reply to that of Esch (q.v.). Fellner insists upon the fact that the "feminine sexual lipoid," previously described by him, is the specific secretion of the ovary. The characteristic lipoid can be demonstrated in the **placenta,** the **corpus luteum,** the interstitial cells of the ovary, and the **testis,** but not in any other tissue. Its subcutaneous injection in animals produces enlargement of the uterus, oestral changes in the endometrium, and hypertrophy of the breasts. Fellner criticizes the well-known work of Seitz, Wintz, and Fingerhut, who isolated from the corpus luteum two substances which predominate at different phases of the corpus luteum cycle and the physiological action of which is quite antagonistic (lipamin and luteolipoid). He alludes briefly to some interesting studies which he and Neumann had carried out on the effect of x-rays upon the ovaries of pregnant rabbits. These appear to indicate a definite secretory role for the interstitial cells.—E. N.

Does our present knowledge of the structure and function of the OVARIES support the theory of the internal secretion of the CORPUS LUTEUM and the INTERSTITIAL GLAND (Stützt unsere jetzige Kenntnis über den Bau und die Theorie der inneren Sekretion des Corpus Luteums und der Interstitiellen Drüse)? Garlund (W.), Zentralbl. f. Gynäk. (Leipsic), 1918, **42**, 649-663.

The author reviews the evidence for the internal secretory activity of the corpus luteum and the interstitial glands, and finds that it is, on the whole, inconclusive. For example, he believes that the premenstrual swelling of the endometrium, commonly attributed to the activity of the corpus luteum, might just as logically be explained as due to the periodic hyperemia associated with the maturation and later nidition of the ovum. He also finds fault with the view of Fraenkel that the corpus luteum exerts a trophic control over the uterus, for, as he says, the uterus is not atrophic in those animals which have no periodic corpus luteum of menstruation. As a result of the study of sudan-stained tissue he believes that many of the histological changes in the corpus luteum and interstitial glands are explainable as granulation processes. He argues also that it is unnecessary to assume a specific hormone activity because of the finding of sudan-stained lipoid granules, and that this assumption is not justified either on histological, clinical or experimental grounds. The article is decidedly hypercritical, but quite suggestive.—E. N.

Experimental physiological action of OVARIAN extracts. Goñalons (G. P.), Surg. Gyn. & Obst. (Chicago), 1918, **26**, 196-206.

After reviewing the work of previous investigators upon the influence of ovarian extracts on the circulation, Goñalons reports the results of his own personal studies. He used macerated decoctions and extracts in different solvents—alcohol, chloroform, ether—of ovaries without corpus luteum and of the corpus luteum of the cow; and from animals of 1, 2 and 3 years. The ovaries were used as quickly as possible after being obtained from the slaughter houses, in some cases in 3 or 4 hours, in others within 12 hours. In the latter case they were preserved in a refrigerator at 0°C or frozen. Maceration was effected with physiological solution or Ringer-Locke fluid 1:4 or 1:5, triturated, macerated during one-half to one hour and then filtered through cotton. Decoctions were made by boiling 5 or 10 minutes. The author has noted no difference in the actions of corpus luteum extract from gravid and non-gravid animals. Immediately after the injection of doses of 20 cc. of maceration or decoction of gravid corpus lutuem at 1:4 or 1:5, there is a marked hypotension of 50, 60, 70 or even 80 mm. of mercury. The pressure falls rapidly, cardiac pulsations are generally considerably weakened, and there are sometimes in the first moments deep convulsive

respirations. After 1, 2 or 3 minutes the pulsations strengthen and the pressure rises. This is relatively rapid at first. After 5 or 10 minutes the pressure returns to normal. Respiration is momentarily accelerated, then becomes normal. The effect on the heart is a diminution in the amplitude, with generally a tachycardia. In rabbits toxic or subtoxic doses cause peristaltic contractions perceptible beneath the skin. The uterus of guinea pigs shows a marked hyperemia. Finally, the author reports clinical and experimental evidence as to what he considers a strongly galactogogue action of ovarian extracts.—E. N.

(OVARY) Corpus luteum and the periodicity in the sexual cycle. Loeb (L.), Science (Garrison, N. Y.), 1918, **48**, 273-277.

This paper is largely a review of the work of the author and others upon the subject. "We can at least be certain that the living corpus luteum has the function of inhibiting ovulation and of being a decisive factor in the mechanism of the sexual cycle."—Chem. Abst., **14**, 970.

On the physiological correlation between the OVARIES and the uterus (De la corrélation physiologique entre les ovaires et l'uterus). Nielsen (F.), Compt. rend. Soc. de biol. (Paris), 1921, **85**, 368-369.

Using the method of Leo Loeb, the author studied the reactions of the rabbit's uterus against intervention, under different physiological conditions. (1) When the uterine segment was opened 3 to 7 days after ovulation, when the corpus luteum should be developing in the ovary, "placentomes" appeared at the point of opening. (2) Contrary to Loeb's findings in the guinea pig, irritation of the mucosa with a glass rod 3 to 7 days after ovulation never caused decidual alterations in the rabbit. (3) When the operation was made 3 to 7 days after copulation, not having given place to ovulation and consequently without the formation of the corpus luteum, no "placentomes" were formed, but "pseudoplacentomes"; recurving of the edges of the incision toward the mesentery, and the simultaneous "prolabation" of the uterine mucosa, presenting a diffuse hypertrophy. (4) Extirpation of the ovaries or of the newly formed corpora lutea at the time of opening the uterus, 3 to 7 days after ovulation, is followed by the formation of "pseudoplacentomes" analogous to those mentioned above. (5) In castrated females treated before and after opening the uterine segment with extracts of corpus luteum as well as extract of the ovarian interstitial gland, intravenously, the opening of the uterine segment gave rise to the formation of "pseudoplacentomes," while opening the uterine wall was followed by cicatrisation without prolapsus or hypertrophy of the mucosa.—T. C. B.

A further study of the end-results of the conserved OVARY. Polak (J. O.), Am. J. Obst. (New York), 1918, **78**, 199-211.

Polak refers to a previous study of 132 cases, from which he concluded that a conserved ovary, if unhealthy, will leave the patient in a worse state mentally, nervously and physically than if total extirpation had been done; that total ablation is preferable at or near the **menopause**; and that the symptoms of the operative menopause are less after extirpation for pelvic inflammation than when the ablation is done for fibromyomata. The present paper is based on a study of the pathology found in 73 re-operations for clinical suffering and subsequent disease in the retained ovary. Polak describes a technic for the conservation of the ovary after removal of the **uterus**, without interfering greatly with the blood supply of the ovary. From the study of more than 300 patients followed for 5 years, he finds that the average duration of the ovarian function after hysterectomy is not over 2 years, and that within that time, flushes and dizziness occur in the large majority. The fact that 73 women had to be re-operated upon within 5 years convinces Polak that routine conservation of the ovary or a part of the ovary, when the uterus has been removed, is not always in the best interests of the woman. The lesions which were found in the retained ovary at re-operation were multiple cystic changes, cirrhosis, cystic formation, infection, and thin-walled cysts with dense adhesions.—E. N.

(THYROID) The medical treatment of Graves' disease, with special reference to the use of CORPUS LUTEUM extract. Hoppe (H. H.), J. Nerv. & Ment. Dis. (New York), 1918, **47**, 254-261.

The theory on which Hoppe bases the use of extract of corpus luteum in Graves' disease is that the latter and hyperthyroidism are synonymous terms, that the internal secretion of the corpus luteum has an inhibitory effect on the thyroid, and that hyperthyroidism is an expression of a dysfunction of the corpus luteum in the female and of the interstitial glands of the **testis** in the male. He is apparently willing to accept the view of Claude and Gougerot that Graves' disease is due to hypovarial disease. He has treated about 20 cases of Graves' disease according to this plan. He found the combination of quinine hydrobromate, ext. belladonnae and ext. corpus luteum to be rapidly beneficial in nearly all the cases. He considers the corpus luteum to be the active therapeutic agent.—E. N.

The absence of PANCREATIC secretions in sprue and employment of pancreatic extract in the treatment of the disease. Brown (T. R.), Am. J. M. Sc. (Phila.), 1921, **161**, 501-507.

Brown has found a complete absence of pancreatic secretion in all five cases of sprue studied. In all instances, he gave pancreatic.

or some form of pancreatic extract, in five to ten grains dose along with twenty to forty grains of calcium carbonate or lactate three times daily two hours after the larger findings. Marked improvement occurred in four cases presented as long as treatment was continued. This was true of one case which was under observation for several years. Her well being is absolutely dependent upon the administration of the pancreatic ferment. The fifth case showed no benefit from this treatment.—J. F.

Cystadenoma of PANCREAS (Zystadenom des Pankreas). Ghon, München. med. Wchnschr., 1921, **68**, 1134.

Of no endocrine interest.—J. K.

Cysts of the PANCREAS. Judd (E. S.), Collected Papers Mayo Clinic, 1920, **12**, 406-415. (Reprinted from Minnesota Med., 1921, **4**, 82-90).

A discussion of the frequency and a general discussion of the pathology, clinical features, and treatment of cysts of the pancreas. The paper is based upon a series of forty-one cases that occurred in the Mayo Clinic. The conclusions are that the condition is rare, does not produce a definite syndrome, is associated with gall bladder diseases in more than one-third of cases, and is amenable to surgical procedure.—J. F.

PANCREAS tumors (Zur Klinik der Pankreastumoren). Kleinschmidt (K.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 1162-1163.

Of no endocrine interest.—J. K.

PANCREAS and HYPOPHYSIS. Kraus (E. T.), Wiener klin. Wchnschr., 1921, **34**, 505.

Data reported elsewhere.

Diagnosis and treatment of diseases of the PANCREAS with special respect to diabetes (Diagnostiek en interne therapie von pancreasstoorniseen en met bijzondere betrekking tot de diabetes). Peutz (J. L. A.), Inaug. Diss. (Utrecht), 1921.

An excellent review of the literature with beautiful microphotographs. The author states that although the pancreas has an influence on sugar metabolism yet there are many cases of diabetes in which no change in the pancreas is observed. The pancreas may be the seat of the origin of diabetes, but certainly it is not the only organ able to produce diabetes mellitus.—J. K.

Studies on PANCREATITIS (Beiträge zur Lehre von der Pankreatitis). Schoenig (F.), Mitt. a. d. Grenzgeb d. Med. u. Chir. (Jena), 1921, **34**, 101-111.

Of no immediate endocrine interest.—J. K.

Totalsequestration des PANCREAS. Schütt, Berl. klin. Wchnschr. 1921, **58**, 1012.

A patient of 52 gradually became ill with pain in the upper abdomen, intermittent constipation and fever. There was a fluctuating tumour in epigastrium. The urine contained 5% of sugar. At operation a large abscess cavity was found between the stomach and liver; the bottom of the abscess was formed by the necrotic pancreas. Recovery followed.—J. K.

PANCREAS concretions (Konkrementbildungen im Pancreas). Simmonds, Berl. klin. Wchnschr., 1921, **58**, 1013.

In 8 of 11 cases of pancreas stones the patients died of coma diabeticum. It is perhaps possible to diagnose these cases by radiography.—J. K.

The PANCREAS in Hodgkins disease and DIABETES of old age (Le pancréas dans la maladie de Hodgkin et dans le diabète aucré des vieillards). Sloboziano (H.), Ann. méd. (Paris), 1921, **9**, 362-376.

A histological study of the pancreas of 9 patients. In one person with Hodgkin's disease the organ was found to be pathological. In the 8 cases of senile glycosuria the pancreas was also pathological.
—F. S. H.

Investigations on the hydrogen-ion concentration of blood after the copious ingestion of acids or of bases, and during the tetanic attacks following the extirpation of the PARATHYROID glands (Recherches sur la concentration du sang en ions hydrogène apres ingestion abondante d'acides ou de bases, et pendant les attaques tétaniques consecutives a l'extirpation des glandes parathyroïdes). Ege (R.) & Henriques (V.), Compt. rend. Soc. de biol. (Paris), 1921, **85**, 389-391.

The greater part of the report deals with changes in pH in the blood of normal goats and dogs. Ingestion of acid (HCl) over a twenty-four day period, displaced the pH decidedly to the acid side. On the other hand, sodium bicarbonate shifts the pH to the alkaline side. Of endocrine interest is the fact that after removal of the parathyroids and thyroid, during attacks of tetany the pH is reduced below the normal, agreeing very well with that found in man during intense musular work.—T. C. B.

(PARATHYROID) General osteitis fibrosa. Fraenkel (E.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 1147.

In this case one of the parathyroids weighed 4.9 gm. Histologically, the tumor consisted of normal parathyroid tissue. The author believes that the experimental work on **tetany** has only a very limited clinical value. He has almost never found pathological changes in cases of tetany. When it is true, as experiments have shown, that the parathyroids have an influence on **calcium metabolism**, it is possible that there really exists a relation between parathyroids and osteitis fibrosa. However, only very few cases are known. A similar case has been reported by O. Meyer.—J. K.

(PARATHYROID) Report of a case of tetany after the third partial thyroidectomy. Gessner (H. B.), New Orleans M. & S. J., 1921, **74**, 382-384.

The case is interesting in that the symptoms were very severe and that parathyroid, as well as calcium, medication failed to relieve them. When bromid was added to the calcium the symptoms were ameliorated.—R. G. H.

Transplantation of PARATHYROIDS in paralysis agitans (Ueber die Transplantation von Nebenschilddrüsensubstance bei der Paralysis agitans). Kühl (W.), München. med. Wchnschr., 1921, **68**, 1083-1084.

In a case of Parkinson's disease the author prescribed tablets of parathyroid, as recommended by Camp, without any success. In another case, however, a splendid result was obtained by transplanting two parathyroids of the calf. (It may be noted that this case was operated on the 5th of July, 1921, and has been reported on the 26th of August).—J. K.

(PARATHYROID) General osteitis fibrosa. Simmonds, Deutsche med. Wchnschr. (Berlin), 1921, **47**, 1147.

In this case there was a **struma parathyreoidea**, the size of a hazelnut. The author considers this goiter as the cause of the bone disease, and compares this to the acromegaly which is caused by a struma of the **hypophysis**. It would perhaps be possible in cases of osteitis fibrosa to examine the parathyroid in a surgical way and to remove tumors when present.—J. K.

A note on the cytology of the PINEAL body of the sheep. Jordan (H.), Anat. Rec. (Phila.), 1921, **22**, 275-285.

The "interneurogliar cells" of the pineal body of sheep from four to eight months of age are characterized by an abundance of small spherical mitochondria and a variable number of larger lipoid globules. These lipoid globules constitute the only cytologic evidence indicative of a secretory activity.—W. J. A.

New studies on the PINEAL gland (Neue Studien über die Zirbeldrüse). Marburg (O.), Arb. a. d. neurol, Inst. a. d. Wien Univ. (Leipzig and Wien), 1920, **23**, 1-35.

An article which contains many interesting statements, but which should be read with a critical sense. The author holds that the pineal is definitely an endocrine organ having an influence on sexual precocity, metabolism and the vasomotor activities. It is stated that hyperfunction of the pineal induces adiposity. Certain therapeutic suggestions are made, which, however, do not seem to be founded on more than inference.—J. K.

Tumor of the PINEAL gland. Morquio (L.), Arch. Lat.-Am. de Pediat. (Buenos Aires), 1919, **13**, 119-127.

Morquio's patient was a boy of 12, previously healthy until he began to complain of headache and the clinical picture of tuberculosis meningitis became installed, quite typical, except that the spinal fluid seemed to be normal. The child died at the end of a month, and necropsy revealed sarcomatous changes in a tumor in the pineal gland, probably of congenital origin.—See also Endocrin., **3**, 78. —J. Am. M. Ass., **73**, 156.

PLACENTAL tissue as a galactogogue. Cornell (E. L.), Surg. Gyn. & Obst. (Chicago), 1918, **27**, 535-538.

The preparation used by Cornell is made from the placenta of cows. The placenta is washed and dried, and then put up in 5 grain capsules. The dose found most satisfactory is 5 grains four times a day. The first dose is given as soon as the patient is able to take nourishment and has had a rest from labor, usually within 12 hours after delivery. No bad effects were noted on the gastro-intestinal tract, although some few patients objected to the odor of the preparation. A table is given showing the results obtained in 100 cases. The study seems to have been satisfactorily controlled. The author concludes that placental tissue has a favorable effect on the production of milk. The nationality or age of the patient plays no part, nor does the sex of the baby. Eighty-seven per cent of the babies whose mothers had received placental tissue began to gain on the fourth and fifth days, against sixty-nine per cent whose mothers did not receive the medication. Forty-four per cent of the experimental subjects regained their birth weight before leaving the hospital against twenty-four plus per cent of the controls.—E. N.

Cytological studies on the internal secretory functions in the human PLACENTA and decidua. Fujimura (G.), J. Morphol. (Phila.), 1921, **35**, 485-578.

A comprehensive study from the cytological viewpoint. An extensive bibliography is appended. Abundant morphological evi-

dence is adduced to show that the placenta is a source of internal secretions. This is true, however, only for the earlier months of pregnancy. Later there is little to indicate the possession of endocrine functions. The epithelium and stroma of the chorionic villi, the decidual cells and the uterine glandular cells, which constitute the chief tissue elements of the placenta and decidua, have received minute attention. All of these show the formative elements of secretions such as plastosomes, lipoid granules and vacuoles. All, except the last, are believed to form internal secretions. The manner of the formation and the discharge of the secretions is described. It is noted that, of all the secretions, those which come from the syncytial layer, decidual cells, uterine glandular cells (a part) and also probably from the Langerhans' islets are absorbed by the mother's body, while those which pass from the ordinary Langerhans' cells and the stroma of the villi are absorbed by the fetus. It has been believed by several authors that the epithelium of the chorionic villi probably serve as an organ by which nutrition is taken up by the embryo; Fujimura, however, states that histologically it is impossible to find any ground for such belief.—W. J. A.

The importance of renal glycosuria for the early diagnosis of PREGNANCY (Ueber die Verwendbarkeit der renalen Schwangerschaftsglykosurie zur Frühdiagnose der Gravidität). Nürnberger (L.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 1124-1126.

Frank and Nothmann have stated that alimentary glucosuria after the ingestion of 100 grams of glucose may often be a very early symptom of pregnancy. The difference between this glycosuria and the glycosuria as seen in cases of diseases of the **liver**, latent diabetes, **thyrotoxicosis**, etc., is that in pregnancy the rise of the blood sugar after 100 gm. glucose remains within normal limits. Nürnberger has confirmed these statements in studies of 71 patients. In all cases the symptom described by Frank and Nothmann was positive. In one case of pregnancy a pathological hyperglycemia after ingestion of glucose was found. In another case the reaction was positive without pregnancy. In cases of abortion the reaction remained positive as long as large parts of the **placenta** in the uterus were in connection with the uterine wall. When, however, the embryo lies loose from the uterine wall the reaction is negative.—J. K.

Action of PROSTATE extracts. Sellei (J.), Ztschr. f. Urol., 1918, **22**, 183.

Prostate extracts had no action on the prostate itself, and in other respects their action was barely appreciable.—Phys. Abst., **3**, 144.

SCLERODERMA ameliorated by thyroid (Sclérémie des adults, amélioration par le traitement thyroïdien). Darier, Ferrand & Mir-

couche (Mlle.), Bull Soc. franç. dermat. et syphil., 1919, —, —, (No. 5); Abst., Schweiz. med. Wchnschr. (Basel), 1919, **50**, 1052.

A case is reported of generalized scleroderma following shock and grippe. There was no sclerodactyly. Improvement followed the administration of thyroid.—R. G. H.

SCLERODERMA. Pulay (E.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 1247.

Demonstration of a case of scleroderma with sclerodactyly. Pathogenesis is unknown; in this case the **generative organs** were hypoplastic, **menstruation** was irregular, the calcium content of the blood was increased and there was much perspiration. Dysfunction of the **thyroid** is probable.—J. K.

SCLERODERMA. Viehweger, München. med. Wchnschr., 1921, **68**, 861.

The author studied the Abderhalden reaction in some cases of scleroderma. In one case the reaction was positive with **thyroid**, in the others with **hypophysis**. In one of these patients a good effect was obtained by intramuscular injection of extract of hypophysis. It was never possible to detect **adrenalin** in the blood with the Meltzer-Ehrmann reaction.—J. K.

The SPLEEN and digestion: Study I. The spleen and gastric secretion. Inlow (Wm. De P..), Am. J. M. Sc. (Phila.), 1921, **162**, 325-348.

The author presents a comprehensive review of the literature upon the role of the spleen in digestion. This is followed by the presentation of his experimental data and his conclusions. His data on gastric secretion were obtained upon three dogs with accessory stomach pouches (secretion meal of meat) before and after splenectomy and on two similar dogs serving as controls. Removal of the spleen in these experiments caused no noteworthy changes in gastric secretion except a slight diminution in the quantity of gastric juices obtained. The author concludes from his data and the review of the literature that a definite pepsinogenic function of the spleen has not been demonstrated and that the relation is probably merely vascular.—J. F.

Transplantation of the TESTICLES (Zur Frage der freien Hodentransplantation). Haberland (H. F. D.), Zentralbl. f. Chir. (Leipz.), 1921, **48**, 993-994.

Haberland has used a disk cut from the testicle for transplantation as recommended by Payr. He performed this operation in hares and has noted that when such a disk was removed the sexual functions remained normal or became normal some time

later. In one animal a disk was removed from one testicle; the sexual functions returned 2½ months after the operation. When such a disk is transplanted it is always resorbed after a time. Still this is no ground for holding that transplantation would be useless. The author suggests the idea that whilst the graft is resorbed other endocrine organs may take its function. In double castration this process is too acute to enable the other endocrine organs to assume the functions of the testicles. As the structure of cryptorchid testicles is not identical with the structure of a normal organ, transplantation of cryptorchid testicles is not recommended.—J. K.

(TESTES) Case of melancholia treated by Steinach's operation (Ueber eine nach Steinach operierte Melancholie). Kramer, München. med. Wchnschr., 1921, **68**, 194.

A report of a case of melancholia in which double vasectomy was performed, with consequent amelioration. From the short description afforded, however, one is led to the opinion that this success is rather due to the optimism of the author than to a real improvement of the patient.—J. K.

(TESTES) A case of melancholia treated by vasectomy (Eine nach Steinach operierte Melancholie). Kramer, Deutsche med. Wchnschr., (Berlin), 1921, **47**, 1082; Berlin klin. Wchnschr., 1921, **58**, 1058.

The patient, a man of 59 with a severe melancholia, was suffering from hypertrophy of the prostate, sexual impotence and moderate glycosuria. Bilateral vasectomy was performed. Immediately after the operation restlessness, agitation, irritability and negativism appeared. After two months marked improvement was evident. The patient became brighter, gained weight and had more appetite, slept better, again had erections and once even an ejaculation. The urine was free from sugar. After the demonstration of this patient Wiener reported that he had treated the patient and has noted a spontaneous remission. The patient is not cured; the glucosuria had disappeared many months before the operation. Lowry has also observed the same patient and does not consider him as cured.—J. K.

(TESTES) Transitory sexual impotence in conscripts and its cure (Impotencia sexual transitoria en conscriptos y su curacion). Lopez (Julio A.), Semana méd. (Buenos Aires), 1921, **28**, 350.

The author has observed that sexual impotence is quite frequent in young conscripts of 20 years. He attributes this condition to intoxication from alcohol and tobacco. The oral administration of testicular substance produced benefit.—B. A. H.

(TESTICLE) Thyrogenital pluriglandular dystrophy (Distrofia pluriglandulare prevalentemente tireo-genitale a tipo di juvenilismo persistente). Mariotti, Riforma med. (Naples), 1919, **35**, 590-596.

Mariotti reports a case of testicular dystrophy with definite symptoms of pituitary hyperactivity and thyroid insufficiency in a man aged 21. A portion of a healthy testicle removed from a man in whom total emasculation had been performed on account of epithelioma of the penis was grafted beneath the skin of the flank and was followed by a rapid improvement in the genital functions. The improvement, however, was confined to the genital sphere, and was of short duration. At the end of a year no trace of the testicular graft remained, and the patient's condition had become the same as before. Mariotti regards the failure of the operation as an additional argument for maintaining the pluriglandular origin of these syndromes. In such cases it is best to treat the cause of the dystrophy, which in the present case was tuberculosis.—Med. Sc. Abst. & Rev., **2**, 135.

TETANY. Bossert, Berl. klin. Wchnschr., 1921, **58**, 1055.

Of no endocrine interest.—J. K.

THYMUS (Dermatosis und innere Sekretion). Brock, München. med. Wchnschr., 1921, **68**, 191.

The author believes that there exists a relation between psoriasis and the thymus. Especially in psoriasis, but also in lichen ruber planus, ichtyosis, etc., he recommends exposure of the thymus to x-rays.—J. K.

(THYMUS, THYROID) Goiter heart and cardiac changes in status thymicolymphaticus (Zur Frage des Kropfherzens und der Herzveränderungen bei Status thymicolymphaticus). Fahr (Th.) & Kuhle (J.), Virchow's Arch. f. path. Anat. [etc.] (Berlin), 1921, **233**, 286-301.

Report of six cases in three of which there were myocardial changes. In the gross the major characteristics were cardiac dilatation and paleness of the muscle. Microscopically there were found round cell infiltrations of varying intensity associated with increased numbers of eosinophils and inflammatory edema. Degenerative changes in the muscle cells and vessel walls as noted previously by Wiesel were also observed. The authors think these myocardial changes are manifestations of the action of a systemic toxin and that the entire anatomical picture of status thymicolymphaticus is best interpreted as only a symptom of some still unknown chemical change.—D. M.

(THYMUS) Roentgen therapy in intrathoracic lesions with special reference to status thymolymphaticus. Meyer (W. H.), Arch. Pediat. (New York), 1921, **38**, 572.

Retrogression of the thymus with clinical cessation of symptoms is obtainable within a period of from one to four months. Providing dosage be exact, failure of symptomatic relief suggests an error in diagnosis. The effect of properly measured roentgen dosage on the thymus appears so definite that it might be applied as a diagnostic procedure in doubtful cases. Meyer gives the technic as used at the New York Post Graduate Hospital. Improvement was noted in nearly every case of thymus involvement.—M. B. G.

The influence of exposure of the THYMUS to x-rays on the excretion of uric acid (Ueber die Beeinflussung der Harnsaüreausscheidung durch Röntgenbestrahlung der Thymusdrüse). Pother & Szego Wien. klin. Wchnschr., 1921, **34**, 386.

The authors submitted the thymus of normal individuals and of patients with Graves' disease to the action of x-rays. In some cases of Graves' disease the excretion of uric acid was increased after this treatment. It is stated that this increased quantity of uric acid is a proof of an enlarged thymus.—J. K.

Lipoma of the THYMUS (Zur Lehre der Thymuslipome). Yamanoi (S.), Zentralbl. f. Chir. (Leipz.), 1921, **48**, 785-787.

A lipoma of the thymus was found in a woman dying of uraemia. This is the second case described.—J. K.

(THYROID) Manic depressive psychosis (Manisch-depressives Irresein). Arndt, Deutsche med. Wchnschr. (Berlin), 1921, **47**, 1180.

Arndt believes that this disease is due to an endocrine disturbance, especially of the thyroid. Therefore, psychotherapy has so little success.—J. K.

The relation of normal rats with and without THYROID feeding and of thyroidectomized rats to oxygen deficiency (Das Verhalten von normalen, mit Schilddrüsensubstanz gefütterten und schilddrüsenlosen Ratten gegen reinen Sauerstoffmangel). Asher (L.) & Duran (M.), Biochem. Ztschr. (Berl.), 1920, **106**, 254-274.

The authors have carried further the work of Streuli, who showed that normal, thyroidectomized and splenectomized rats behave differently in the presence of a deficiency of oxygen. Normal and thyroidectomized rats behave nearly alike and withstand reduced oxygen pressure well, while splenectomized rats are much more sensitive and more injuriously affected. In addition to confirming Streuli's results they add their results on the effect of thyroid feeding. The method consists of putting the animals under a bell jar, gradually reducing the pressure and noting the behavior of the animal, particularly as regards its respiration. They report in detail

three experiments carried out on thyroidectomized rats and five experiments on normal rats which had been fed with thyroid. They find that normal rats fed with thyroid are as sensitive to reduced oxygen pressures as are splenectomized rats. This effect was detectible in five days after beginning the feeding. They point out that inasmuch as thyroid feeding produces the same effects as splenectomy that this is further possible evidence of an antagonistic action between the thyroid and spleen and that this phenomenon may have some bearing on the etiology of Basedow's syndrome. They further point out that the effect of thyroid feeding on the ability of rats to withstand oxygen deficiency could be used as a biological test for the pharmocological activity of desiccated thyroid.

—D. M.

(THYROID) Hyper- and hypo-thyroidism; causation, prevention and treatment. Barr (J.), Practitioner (London), 1921, **106**, 381-399.

The author, for instance, has "long since discarded" x-rays or operative treatment of exophthalmic goiter, believing that "simpler, less expensive and more effective methods should suffice." Of the latter he strongly advocates Albert Abram's concussing of the 6th and 7th cervical spines, as a means of contracting the left ventricle and making far more effective systole. The hyperactive calcium metabolism should be diminished. Alkalinization of the blood is advised. Phosphoric and citric acids as decalcifying agents are recommended. In early cases of hypothyroidism iodine is our sheet anchor; in advanced cases thyroid extract should be added, and where there is retention of calcium salts, decalcifying agents should be administered. Barr regards adenoids as due to defective thyroid function and believes that a lump of solid iodine should be placed in a current of air in the children's dormitory as a prophylactic. Enlarged prostate is considered analagous to a large fibroid goiter and associated with defective thyroid function, and thyroid extract, iodides and decalcifying agents and restriction of lime intake, is indicated. (A jolly, chatty article, more entertaining than scientific).—H. L.

(THYROID) Iodine in the treatment of goiter. Beebe (S. P.), Med. Rec. (New York), 1921, **99**, 996-999.

The importance of the iodine content of the thyroid normally and in the goitrous gland is discussed. The author then states that in his experience three different forms of iodine answer all the requirements for therapeutic purposes, namely, potassium iodide, ferrous iodide, and thyroid extract. The writer has never been able to find any advantage in the large array of ointments, organic compounds of iodine, or so-called colloidal preparations of iodine available in the market. He has had no experience with Kendall's thy-

roxin. Beebe strongly deprecates large doses of iodide in any form of goiter, even ten grains three times daily. In endemic or simple goiter one or two grains three times daily should be used at first, gradually increased to five grains three times daily; rarely, if ever, is it necessary to give larger doses. Beebe does not favor the large doses advocated by McCarrison. Furthermore, the iodine should be administered for a long time, months and even years. Quite opposed to prevailing opinion, the writer believes iodine to be one of the most valuable therapeutic agents we have in the treatment of the hyperthyroid forms of goiter. If the dose is properly regulated there need be no fear of iodine Basedowism. The hyperplastic gland is poor in iodine—0.095 milligrams per gram of fresh gland, as against 0.364 in normal thyroids. The dosage recommended is one-half to one grain of potassium iodide three times daily to begin with and for several weeks or months following. Especially is iodine beneficial in women who have had exophthalmic goiter for several years. "No other medication can replace iodine in this group."

—H. L.

(THYROID) Exophthalmic goiter as a cause of sterility (L'accroissement d'une cause de stérilité féminine depuis la guerre par le développement de la maladie de Basedow). Blondel (R.), Bull. Acad. de méd. (Paris), 1919, 3.s., **82**, 185-188.

Blondel comments on the prevalence during the war of the emotional factors known to co-operate in the production of exophthalmic goiter, and remarks that he has not been surprised to find hyperthyroidism much more prevalent now than in former years, especially in women. Any one of the main symptoms, the exophthalmos, the tachycardia, tremor or goiter, may alone reveal the excessive functioning of the thyroid, and explain any one of numerous trophic and other changes. Chief among these he has noticed a decrease in the size of the uterus. This atrophy of the uterus is possibly the explanation of sterility in certain cases, and as such the causal hyperthyroidism should be combated. There are several ways of doing this, raying the thyroid, injecting serum from thyroidectomized animals, thymus treatment, and other means. He prefers **thymus** treatment, and has been using it for years as the routine treatment in exophthalmic goiter. He gives half a raw thymus from a lamb, chopped and mixed with a little flour, salt and butter to make small balls that are mixed with soup as it is eaten. Subcutaneous injection of the extract is more active, but less convenient for the patient. Thymus treatment is logical, he reiterates, on account of the antagonism between the thymus and thyroid, and years of experience have proved the soundness of these premises. He warns in conclusion that we must be wary in giving iodine in cases of amenorrhea or we may whip up an incipient exophthalmic goiter. The thymus treatment in these cases of sterility might be supplemented by massage

of the uterus and dilation with laminaria for three or four days, each month or two months. The pathologic condition does not seem to be able to right itself spontaneously but with this treatment perseveringly carried out good results were obtained in the majority of his cases.—J. Am. M. Ass., **73**, 1808.

THYROIDITIS in scurvy (Thyroïdite au cours du scorbut). Bonnet (P.), Gaz. d. hôp., 1920, **93**, 376; Abst. Med. Sc. Abst. & Rev. (Lond.), 1920, **3**, 10.

Bonnet reports the case of a Roumanian farmer who developed acute suppurative thyroiditis during an attack of scurvy. The localization of the infection in the thyroid was probably due to small hemorrhages in the gland becoming infected from the septic buccal cavity.—R. G. H.

Report of a case of INFANTILISM with rickets. Boyd (D. H.), Penn. M. J. (Harrisburg), 1921, **24**, 870-875.

A remarkable case of infantilism in a girl of 9 years is reported. There were some bony changes and other symptomatology of rickets, but also complete filling of the sinuses with solid bone, and absence of sella turcica in x-ray plates. Pancreatic efficiency tests gave normal results and feeding with pancreatic extracts was unsuccessful. The patient did not correspond to any of the recognized endocrine types, such as infantile myxedema, Froelich's preadolescent hypopituitarism or Lorain infantilism. Some of the signs and symptoms suggested osteogenesis imperfecta, fragilitas osseum and leontiasis ossea, but none of these diagnoses was warranted. Boyd was finally disposed to consider the case one of intestinal infantilism with rickets and with a secondary hypophyseal involvement to account for the hyperostosis in the skull. Treatment directed to rickets, to **ductless gland** disease and to intestinal infantilism (as advised by Herter), were all ineffectual. Complete autopsy findings revealed hypoplasia or atrophy of the **hypophysis, pineal, thymus, thyroid,** and **adrenals**; amyloid disease of the liver, spleen, and kidney; hemorrhage from intestine, liver, and gall bladder; fatty infiltration of the liver; generalized edema; general hyperplasia of the bony structures of head, face, ribs, and extremities, with spontaneous fractures of the left radius and left femur.—H. L.

The influence of THYROID extract on the multiplication of cells (L'action de l'extrait thyroïdien sur la multiplication cellulaire). Champy (Ch.), Arch. de Morph. gén. et expér. (Paris), 1922, **1**, 1-58.

Tadpoles were put into basins of water with large quantities of dried thyroid of sheep. It was observed that when after 48 hours the animals were taken out and placed in clear water, they were "sensibilised." In other words, the effect of the thyroid seemed to

continue. The limb buds, when studied histologically, showed a change in the "coefficient mitotique." This coefficient is obtained by observing, in at least 4,000 cells, the numbers with and without mitosis. It does not vary much in normal tadpoles during growth. In animals treated with thyroid this coefficient for cells in the skin of the limb buds steadily increases until the death of the animal. The same is observed in the muscles and the cartilages of the limbs. In the intestines, however, the opposite is seen. The normal regression with degeneration of epithelium is hastened. In the tongue, esophagus, stomach and thymus, the number of mitoses rapidly increases by thyroid treatment. Proliferation is found in the nervous system, but only for a limited time and in special places, e. g., in the encephalon. These facts are held to prove that extract of thyroid exerts not a general, but a selective influence. Its action depends not only on the presence of a hormone, but also on the local sensibility of the various tissues.—J. K.

(THYROID) Treatment of goiter (Kropfbehandlung). Eiselsberg, München. med. Wchnschr., 1921, **68**, 894.

The etiology of goiter is unknown. The cause should always be sought. Before operation radioscopic examination in two planes is desirable. Only in this way is it possible to get an idea of the shape of intrathoracic goiters. Almost complete thyroidectomy is advisable. The danger of **tetany** is not negligible. When it occurs it is advised not to begin with parathyroid transplantation, but to try injections of afenil, lactate of calcium up to 30 grams daily, and clysmata with chloral hydrate. When transplantation is necessary the organs ought to be taken from children dying at birth. Histological examination of the organ is necessary. Even slight tetany has a doubtful prognosis, as the symptoms may rapidly increase. The best treatment of Graves' disease is resection of the thyroid. Thymectomy, according to the author, not necessary. The operation should be performed under narcosis; the patient should take calcium lactate a long time before the operation, and be kept quiet. The author considers the thyroid as the primary seat of Graves' disease. —J. K.

The THYROID gland and exophthalmic goiter. Foss (H. L.), Penn. M. J. (Harrisburg), 1921, **25**, 35-39.

A concise, conservative summary of our present knowledge of the thyroid, especially directed to a consideration of the diagnosis and surgical treatment of Graves' disease; nothing new is presented, but the review is well written.—H. L.

(THYROID) Observations on the basal metabolism estimations in the goiter clinic of the university hospital. Frazier (C. H.) & Adler (F. H.), Am. J. M. Sc. (Phila.), 1921, **162**, 10-12.

This paper reports the experience of the University (Pennsylvania) Clinic with the portable Benedict apparatus in the study of goiter. The authors conclude that these estimations are of value in following ways: In eliminating those cases which will not be benefited and might be made worse by operation, in offering confirmatory evidence of the degree of toxicity, and in offering a quantitative index for use in diagnosis, prognosis, and treatment.—J. F.

(THYROID) Treatment of goiter with x-ray (Behandeling van struma met Röntgenstralen). Gaarenstroom (G. F.), Ned. Tijdschr. v. Geneesk. (Haarlem), 1921, **65**, 209-214.

In goiter or Graves' disease x-rays nearly always produce an improvement or cure. The vasomotor and nervous symptoms diminish or disappear and metabolism becomes normal. This is particularly true in malignant goiter. The symptoms of pressure rapidly improve, and if no metastases are present splendid results may be obtained. In the 15 cases reported by Gaarenstroom 7 were of the exophthalmic type and 4 were cancerous.—J. K.

(THYROID) Tumors of liver with the structure of a colloid goiter (Lebertumoren vom Typus einer Kolloidstruma). Gödel (A.), München. med. Wchnschr., 1921, **68**, 1003.

From a woman of 21 a colloid goiter was removed. Sixteen years later a tumor was found in the abdomen. It proved to be a colloid goiter in the liver. Some months after this operation the woman died from an embolus in the arteria pulmonalis after childbirth. At post-mortem examination many tumors were found in the liver; all showed the typical structure of a colloid goiter.—J. K.

(THYROID) Intralaryngeale Struma. Gödel (A.), München. med. Wchnschr., 1921, **68**, 1002.

Data are to be reported in full in the Arch. f. Laryngol.—J. K.

(THYROID) Typical changes in the blood under the influence of want of oxygen (Ueber ein typisches Verhalten des Blutes unter dem Einflusz der Sauerstoffmangels). Gutstein (M.), Folia haematologica (Leipzig), 1921, **26**, 211-230.

When too small quantities of oxygen are available for the tissues typical changes in the blood occur. Whether oxygen deficiency is caused by a small quantity of oxygen in the air, as in the mountains, by diseases of the lungs or by destruction of erythrocytes, the changes in the blood picture are the same. As the number of erythrocytes increases the amount of hemoglobin becomes higher, the neutrophilic leucocytes diminish, and lymphocytosis with eosinophilia is observed. But the same blood picture is observed in Graves' disease (not at all typical—J. K.) and hyperthyroidism. We know also that want of oxygen has an influence on the thyroid, for Mansfield and

others have proved that the typical blood picture in the mountains is not observed in animals when the thyroid has been previously removed. Therefore, Gutstein concludes that the influence of a want in oxygen in the blood is mediated through the thyroid, which is stimulated in turn and gives rise to the changes in the blood.—J. K.

Congenital teratoma of the THYROID (Kongenitales Schilddrüseteratom). Hadda, Berlin klin. Wchnschr., 1921, **58**, 1084.

In a new born baby with tumor of thyroid and attacks of suffocation the tumor was removed. Histologically, thyroid tissue, central nervous system tissue, cylindrical epithelium, cells resembling intestinal glands, muscles, and connective tissue were found.—J. K.

(THYROID, THYMUS) X-ray treatment of scleroderma (Zur Röntgenbehandlung der Sklerodermie). Hammer (G.), München. med. Wchnschr., 1921, **68**, 1109-1110.

That scleroderma has some relation to endocrine disorders is made probable by cases of the disorder accompanied by symptoms of Graves' or Addison's disease. In a patient with thyreotoxicosis, who had scleroderma of the hands and forearms, the symptoms disappeared after exposure of the thyroid to x-rays. In another patient with sclerodactyly with changes in the bones no effect was seen from exposure of the thymus and thyroid to x-rays. In a third patient with scleroderma, a small goiter, and now and then tachycardia, a marked improvement followed radiation of the thymus and thyroid.—J. K.

(THYROID) Metabolimetry in hyperthyroidism. Harrower (H. R.), Med. Rec. (New York), 1921, **99**, 1003-1005.

A concise statement of the use of basal metabolism estimation in the diagnosis and treatment of thyroid disease, more especially hyperthyroidism, together with reference to those who are chiefly responsible for the development of this procedure.—H. L.

(THYROID) Maladie de Basedow familiale et héréditaire chez l'enfant. Harvier (P.), Paris méd., 1919, **9**, 457-459.

In Harvier's case the goiter developed at 12, and the young man's mother, grandmother and an aunt on both the maternal and paternal sides had presented exophthalmic goiter. His sister had escaped. The tremor in his case had been noted from early childhood.—J. Am. M. Ass.

Chemical studies of physiology and pathology. Function of the THYROID gland (Chemische Studien zur Physiologie und Pathologie. Zur Funktion der Schilddrüse). Herzfeld (E) & Klinger (R.), München. med. Wchnschr., 1918, **65**, 647-651.

A series of experiments carried out on rats to which was fed a preparation of thyroid proteins iodized by the authors. The results lead to the conclusion that the secretion of the thyroid hormone is not tied up with a protein body, but is concerned with a dialysable decomposition product. The iodine is considered as being in the gland in the form of a salt combination of the protein decomposition product; it is not an actual constituent of the secretion, but its function is rather to facilitate the formation of the secretion. The nerves of the gland act to increase the hydrolytic processes in the cells.
—F. S. H.

Comparative sensitivity to intoxication and infection of animals deprived of the THYROID (Sensibilidad comparada de los animales tiroprivos a la intoxicación y a la infección). Houssay (B. A.) & Sordelli (A.), Rev. Asoc. méd. argent. (Buenos Aires), 1921, **34**, 435.

Thyroidectomy does not modify the sensitivity of the rabbit toward diphtheria bacilli or toxin nor that of the guinea pig toward diphtheria or cobra toxin. The rabbits which have trophic symptoms and a poor state of nutrition are most sensitive.—B. A. H.

Influence of the THYROID on the formation of antibodies (Influencia de la tiroides sobre la formación de anticuerpos). Houssay (B. A.) & Sordelli (A.), Rev. Asoc. méd. argent. (Buenos Aires), 1921, **34**, 438.

Rabbits deprived of the thyroid produce a serum hemolytic toward sheep, more active than that of the controls. Rabbits and horses deprived of the thyroid produce an agglutinating serum slightly more active than the controls (Eberth). The results are more complex in regard to the production of antitoxin for the dog deprived of thyroid produces immune sera (antidiphtheritic and antitetanic) a little more active than those of normal dogs. Rabbits, and above all horses, deprived of the thyroid produce a serum very feeble in power compared to that of controls.—B. A. H.

Histological changes in the central nervous system in THYROIDECTOMIZED cats (Histologische Veränderungen im Zentral-Nervensystem bei Schilddrüsenmangel). Isenschmid (R.), Frankf. Ztschr. f. Path. (Weisb.), 1918, **21**, 321-336.

The cytology of the central nervous system was studied in cats which had been thyroidectomized from two to four months previously. Basic aniline dyes, methylene blue, thionin and toluidin blue were used. Isenschmidt found the most marked changes in the more differentiated cells, as, for example, the motor cells of the anterior horn and the Purkinje cells. He noted particularly a decrease in the number and a shrinkage in the size of the Nissl granules. He points out, however, that such changes as he has observed cannot be

considered as characteristic of thyroid deficiency since similar changes are found in a great variety of intoxications.—D. M.

Creatin metabolism and the THYROID gland (Kreatinstoffwechsel und Schilddrüse). Iseke (C.), Monats. f. Kinderh. (Berlin), 1921, **21**, 337-350.

The author reports a series of studies on the creatin excretion in children, particularly in its relation to thyroid activity. He confirms the presence of a physiological creatinuria in children, disappearing at about the age of 12-14. In a normal infant of 4 months he found that the creatin comprised 87% of the total creatin-creatinin excretion. The creatin excretion was definitely influenced by the degree of thyroid activity present. In cases of myxedema the creatin excretion was diminished or even absent, and he considers this an early and diagnostic test for athyreosis. In a case of hyperthyroidism he found an increased creatin excretion and in myxedema the creatin excretion was increased by thyroid feeding.—C. H. G.

Metamorphosis provoked by the injection of THYROID preparations and of THYROXIN (Kendall) in thyroidectomized Axolotls. Heightened toxicity of iodized combinations in the case of thyroidectomized animals (Métamorphose provoquée par l'infection de préparations thyroïdiennes et de thyroxine (Kendall) a des Axolotls ayant subi la thyroïdectomie. Toxicité élevée des combinaisons iodée dans le cas d'animaux thyroïdectomisés). Jensen (C. O.), Compt. rend. Soc. de biol. (Paris), 1921, **85**, 391-392.

The author has shown that metamorphosis may be provoked in Axolotl not only by specific thyroid substance, but also by injection of iodocasein, iodoserumglobulin and iodoserumalbumin. Intraperitoneal injections of thyroxin (synthetic) also determines metamorphosis. Is this metamorphosis due to the direct effect of the compounds, or is the effect indirect, the compound being absorbed by the thyroid, and transformed? Iodized combinations are very toxic for thyroidectomized axototl: doses too small to effect metamorphosis kill the animal, and therefore the above question must remain unsolved at present. Experiments with thyroxin, however, favor the hypothesis that it is the hormone of the thyroid gland.
—T. C. B.

(THYROID) Struma maligna. Kuijer (J. H.),, Ned. Tijdschr. v. Geneesk. (Haarlem), 1921, **65** (II), 1133-1134.

Demonstration of a case, markedly improved by x-ray treatment.—J. K.

Action of the THYROID and the PARATHYROID glands on respiratory exchange (Action du corps thyroïde et des glandes parathyroïdes sur les échanges respiratoires). Labbé (M.) & Stévenin (H.), Ann. méd. (Paris), 1921, **9**, 264-270.

The authors studied the respiratory exchange in a series of normal, parathyroidectomized and thyroidectomized rabbits, and rabbits to which desiccated thyroid was administered. Two parathyroids were removed from the experimental animals. Although the respiratory quotient for the four groups remained the same within the limits of the methods employed, there is evident from the tabulated results a decided influence on the oxygen consumption and CO_2 production as a result of the procedures described. There is an increase in these factors in the parathyroidectomized and thyroid fed animals and a decrease in the thyroidectomized rabbits. Although the increase is slight in the parathyroidectomized group it seems as valid as are the other variations. The possibility of an antagonistic action of the two glands is expressed.—F. S. H.

THYROID and other endocrine disturbances as viewed by the internist. Lichty (J. A.), Am. J. M. Sc. (Phila.), 1920, **159**, 800-814.

Barly recognition and prompt action are urged for the successful medical treatment of hyperthyroidism. For advanced cases the roentgen ray is recommended as presenting attractive advantages in application.—W. J. A.

The pathogenesis of deficiency diseases: The effects of some food deficiencies and excesses on the THYROID gland. McCarrison (R.), Indian J. Med. Res., 1920, **7**, 633-647.

The effects on the thyroid apparatus of imperfect, ill-balanced and excessive diets have been studied in monkeys, guinea pigs and pigeons. The diets used may be grouped according to their effects on the histology of the thyroid gland under two headings: (1) those that induce a decrease in the size and weight of the thyroid, and (2) those that induce an increase in the size and weight of the thyroid. Under Group 1 (diets inducing a decrease) the following diets were used: (a) autoclaved milled rice, (b) autoclaved rice and butter, (c) autoclaved rice, butter and onion, (d) autoclaved food and onion, (e) autoclaved food and butter and onion. All five of these diets have vitamine deficiencies and all cause a diminution in size and weight of the thyroid. Under Group 2 (diets producing thyroid enlargement) the following diets were used: (a) crushed oats and autoclaved milk, (b) mixed varieties of millet seeds, (c) mixed varieties of millet seeds, peas, butter, with and without onion. The enlargement found in guinea pigs fed on the scorbutic diet of oats and autoclaved milk was found to be due largely to congestion and hemorrhagic infiltration. The thyroid enlargement from overfeeding with millet seeds is a true hypertrophy and hyperplasia. Still more marked hypertrophy and hyperplasia were observed when butter and peas were added to this diet. The addition of onion to this high protein and fat diet appeared to lessen the thyroid hyperplasia. The author believed the beneficial effect of onion in retarding hyper-

plasia is due, in part at least, to its action in restraining the growth of putrefactive bacteria in the gastrointestinal tract and in retarding the absorption of their products; while diets deficient in vitamines render the thyroid gland susceptible to the noxious action of intestinal bacteria or their products, with resultant atrophy and necrotic changes. He seems to have realized the dangers from uncontrollable factors in evaluating the data of such experiments.—D. M.

(THYROID) Simple goiter a public health problem. McCord (C. P.) & Walker (R. C.), Ohio State M. J. (Columbus), 1920, **16**, 501-506.

See Endocrin., **4**, 499.

The THYROID and its diseases. Mayo (C. H.), Collected Papers Mayo Clinic, 1921, **12**, 323-329. (Reprinted from Surg. Gyn. & Obst., 1921, **32**, 209-213).

A review of the progress made in this field. The value of basal metabolic rates, blood pictures, **epinephrin** injections as diagnostic means are discussed as well as the factor which lessens the dangers of operation.—J. F.

(THYROID) Endemic and sporadic cretinism (Ueber endemischen und sporadischen Kretinismus). Melzer, Berl. klin. Wchnschr., 1921, **58**, 1019.

Endemic cretinism is due to geological causes. Sporadic cretinism or infantile myxedema has probably no relation whatever to geological conditions, but is due to degeneration of the thyroid. In endemic cretinism the thyroid often shows hypertrophic degeneration, though normal areas may be found. Sporadic cretinism generally begins in youth and produces symptoms resembling those of myxedema. Thyroid, fresh or in tablets, is beneficial.—J. K.

(THYROID) Case of cachexia strumipriva (Fall von Cachexia strumipriva). Möbius, Berl. klin. Wchnschr., 1921, **58**, 1017.

A man of 36 was operated upon for the third time for goiter. Though a part of the goiter was left behind, **myxedema** developed. The voice became rough, the hair fell out, the patient felt weak and tired, and the skin was swollen and dry. Thyroid tablets had a good effect. The tissue removed showed colloid goiter with much connective tissue. Probably the piece left behind had not sufficient functional capacity to prevent the onset of myxedema.—J. K.

(THYROID) Endemic goiter in Urubamba (Peru) [El bocio endémico en Urubamba (Peru)]. Monge (C.), Cron. Méd. (Lima), 1920, **37**, 394-415.

Monge attempted to determine whether the endemic goiter of Peru is, like that of Brazil, due to a trypanosome and transmitted

by an insect. A study of the blood of sixty persons in the goiter belt of Peru failed to reveal the presence of this organism. Inoculations into animals gave negative results. The drinking water is the principal vehicle of propagation, but there is no danger when it is boiled. The germ of Chaga's disease was never found present.

—A. M. Q.

(THYROID) Basedow's syndrome, and cretinism in Urubamba (Peru) [Syndromes Basedauiano, y cretinismo en Urubamba (Peru)]. Monge (C.), Cron. Méd. (Lima), 1921, **38**, 3-11.

Monge describes different kinds of goiter with hyper- and hypothyroidism, and cretinism as frequently found in Urubamba, Peru.

—A. M. Q.

Diagnostic and clinical aspects of HYPERTHYROIDISM (Diagnostico y aspestos clinicos de hypertiroidismo). Mora Quimper (A.), Cron. Méd. (Lima), 1921, **38**, 170-176.

The author considers the need in the clinic of an early diagnosis of hyperthyroidism at a time when it is quite impossible to find any tumor in the thyroid gland. The different criteria of diagnosis, as Goetsch's ephinephrin test; the changes in the blood sugar; the high metabolic rate; and the variations in the blood picture, before and after the Goetsch test, are very valuable for an early diagnosis of this trouble, as well as for the removal of these patients from the neuropathic group where they are sometimes placed. Some clinical aspects of hyperthyroidism, especially its cardiac and nervous aspects, are considered.—Author's Abst.

(THYROID) Sporadic hemophilia successfully treated with hematoethyroidin. Acute thyroiditis during the treatment (Hemophilie sporadique traitée avec succés par l'hémato-éthyroidine. Thyroidite aiguë au cours du traitement). Oddo (C.) & Mattei (Ch.), Bull. et mém. soc. méd. des hôp. d. Par., 1921, **45**, 1292-1298.

A report of a case concisely described in the title. Hematoethyroidin was given in the dose of 3 spoonfuls in coffee per diem. After 47 hours all hemorrhage had stopped. After 6 days of treatment there was fever, rapid pulse, dysphagia and redness over the right lobe of the thyroid in which could be felt a tumefaction as large as a nut. Exophthalmia was present. On the 7th day the fever began to subside as did the swelling in the thyroid. Epistaxis reappeared, to subside on the readministration of the drug, which again caused the development of the hyperthyroid syndrome. The patient has been under observation now for 2 years and has continually improved.—F. S. H.

(THYROID) Surgery of sub-sternal and intrathoracic goiters. Pemberton (J. de J.), Collected Papers Mayo Clinic, 1920, **12**, 354-375.

A comprehensive clinical surgical paper based upon the experiences of the Mayo Clinic in handling this type of goiter. The results of the operation for removal of these goiters were very satisfactory. The mortality was low and the patients were almost immediately relieved of most distressing symptoms.—J. F.

Gout and THYRO-TESTICULAR insufficiency (Goutte et syndrome thyro-testiculaire). Phronimos (S.), Thése de Paris, 1918.

From a review of literature and a good description of a clinical case the author comes to the following conclusions: Gout and insufficiency of the thyroid and testicles may be observed in one and the same patient, although this combination has, up to the present, never been described. Some years before the patient was attacked with gout, endocrine disturbances were evident in easy fatigue, loss of sexual desires, atrophy of the testicles, and loss of hairs of the axilla and pubes. The administration of testicle extract had a bad effect, when given alone; thyroid was well taken and when combined with testicle yielded a good result. The gout pains were markedly better some time after treatment with thyroid had been instituted. The author states that clinicians should note the possibility of endocrine disturbance in cases of gout.—J. K.

The value of basal metabolism studies in the diagnosis and treatment of THYROID diseases. Rowe (A. H.), Am. J. M. Sc. (Phila.), 1921, **162**, 187-200.

A summary of the literature concerning the clinical value of the test, together with the author's own data. Eighty cases have been studied by the Tissot spirometer-gas analysis method. The author's conclusion serves to re-emphasize the importance of basal metabolism determination in the handling of thyroid diseases. By this method diagnosis of early and obscure cases is facilitated. It is of special value as a guide in treatment.—J. F.

(THYROID) The value of Bram's quinine test as a diagnostic measure for exophthalmic goiter (Sur la valeur du test de Bram a la quinine comme moyen de diagnostic du goitre exophthalmique). Sainton (P.) & Schulmann (E.), Bull. et mém. soc. méd. des hôp. d. Par., 1921, **45**, 1304-1306.

The authors consider that this test should be accepted with only the most severe reservations. This opinion is supported by studies on 10 cases.—F. S. H.

(THYROID) Glycemia and hyperglycemia produced in exophthalmic goiter (La glycémie et l'hyperglycémie provoquée chez les sujets atteints de goitre exophthalmique). Sainton (P.), Schulmann (E.) & Justin-Besançon, Bull. et mém. soc. méd. des hôp. d. Par., 1921, **45**, 1298-1303.

Studies on glycemia in Basedow's disease demonstrate that hyperglycemia is not constant in the disorder and is of low degree: that there is no relation between the glycemia and the intensity of the Basedow's disease, whether it is a question of induced or normal glycemia. The results of induced hyperglycemia, whether produced by ingestion of glucose or injection of **hypophyseal** extract, are inconstant and no different from those obtained in other pathological conditions. **Adrenine** hyperglycemia is more frequent after glucose ingestion, but there is no relation between the reaction and the reaction to **pituitrin** in the same subject. The action of the thyroid in carbohydrate metabolism is an unsolved problem. The occurrence of exophthalmic goiter and **diabetes** has as yet not been proven to be more than coincidence.—F. S. H.

(THYROID) Basedow's disease (Ueber den Morbus Basedow). Schmidt (O.), Mitt. a. d. Grenzgeb. Med. u. Chir. (Jena), 1921, **33**, 512-532.

A highly important study. The author attempted to determine if the distinction between thyroidism and Basedow's disease is an artificial one. He, therefore, examined the blood in these cases. The blood picture in Basedow's, in thyroidism and in normal individuals, whether thyroid is given or not, shows no characteristic difference. R. Schmidt has stated that parenteral administration of proteins produced in Basedow's disease a much more marked thermal reaction than in other conditions. The author could not confirm this. Complement fixation tests with extracts from exophthalmic goiter thyroids or jodothyrin used as antigens proved to be useless. A cutaneous reaction with extracts of exophthalmic goiter thyroids gave no reliable results. However, it was found that the freezing-point of the serum in Basedow's disease is much lower than that of normal sera. In thyroidism it proved to be higher than in normal sera. When the patients with Basedow's disease are kept in bed, the freezing-point shows a tendency to become normal. Operation ought never to be carried out as long as the freezing-point of the serum is not normal. There is another difference between the serum in Basedow's disease and in thyroidism. Kottmann has described the "dispersion power" (Dispergierungsvermögen) of serum. This means the power with which the serum prevents a substance in colloidal state from precipitation. Kottmann used iodide of silver. The technic is as follows: To 1 cc. of serum (taken after a short fast) is added 0.25 cc of 5% K I and 0.3 cc. of 5% Ag NO_2 solution. This is done in the dark. A white precipitate is formed. This is exposed for 10-25 minutes to an intense light. Then 0.5 cc. of 0.25% hydrochinone is added, after which the color becomes red, brown and at last black. In Basedow's disease it takes 5-7 hours before the serum is black; in normal individuals this time is much shorter; in thyroidism still shorter. It is remarkable that in diseases of the **pancreas**, in Addison's disease,

and in hypophyseal disease this time is longer than normal, though never as long as in Basedow's disease. The author concludes that thyroidism is a different disorder from Basedow's disease. He considers thyroidism as an intoxication with incomplete, and Basedow"s disease as an intoxication with excess products of the thyroid.—J. K.

(THYROID) The indications for surgical treatment in the various types of goiter. Sistrunk (W. E.), Collected Papers Mayo Clinic, 1920, **12**, 330-336. (Reprinted from Surg. Gyn. & Obst., 1921.)

All goiters are divided into colloid, adenomatous, and exophthalmic. Colloid goiters in young persons are looked upon as not surgical. In the majority of instances, after patients with adenomatous goiter have attained the age of 25 or 30, surgery is advocated. All adenomatous goiters associated with hyperthyroidism are considered surgical if the condition of the patient will permit an operation. Exophthalmic goiter, according to their experience, is best treated surgically. If care is exercised in selecting the type of operation to be performed in a given case, the mortality following the operation is low.—J. F.

(THYROID) The surgical treatment of goiter (Ueber die chirurgische Behandlung des Morbus Basedow). Sudeck (P.), Deutsche med. Wchnschr. (Berlin), 1921, **47**, 1224-1226; Berl. klin. Wchnschr., 1921, **58**, 1050.

The diagnosis of "Graves' disease," according to Sudeck, is too often made. Especially the diagnosis of "formes frustes" is much abused. He distinguished three types of hyperactive thyroid disease: 1. The classical Graves' disease, with highly vascularized goiter and proliferation of epithelium in the gland. 2. Thyroidism with colloid goiter, with the typical histological picture of a non-vascularizated goiter and no proliferation of epithelium. Often the "thyroid heart" is found. The symptoms are the same as when too much thyroid is administered. They develop more slowly, whilst the real Graves' disease has a more acute character. Though many authors deny a difference between these types, Sudeck maintains that they are not identical. 3. Status neuropathicus. Here there exists often a colloid goiter with symptoms of physical and psychical degeneration. The symptoms are very variable, including abnormal irritability; vasomotor disturbances, headaches, giddiness, tremors, but no exophthalmus. The blood picture as described by Kocher is often found. In this last type surgical treatment rarely is successful. The other types must be treated by ligation of the four arteries and resection of both lobes of the thyroid. In five cases of very serious Graves' disease the author has completely removed the thyroid and given thyroid preparations afterwards. In all these cases the results have been good, though once tetany was seen after the operation. Sudeck does not believe that, though in special cases it

may be necessary, thymectomy is generally indicated. X-ray treatment never has the same splendid effect as operation, and as there are adhesions formed, and cases known in which this treatment produced myxedema, the author warns against it.—J. K.

(THYROID) Observations on goiter. Sweet (P. W.), Northwest Med. (Seattle), 1921, **20**, 105-109.

Sweet classifies goiters as follows: I. Colloid—(a) adolescent; (b) simple colloid. II. Adenoma—(a) non-toxic; (b) toxic. III. Hyperplastic, exophthalmic, always toxic. IV. Carcinomatous. He briefly presents the pathological pictures and symptomatology and clinical course of these types and their differentiation. He believes that the first group are always non-surgical unless pressure symptoms should be very disagreeable. The other three groups he considers always surgical and does not even refer to possible medical or x-ray treatment. The various stages of operative procedure in very toxic cases are mentioned, namely, boiling water injections, preliminary ligation of one or more vessels and finally thyroidectomy.—H. L.

Small THYROID tumor accompanying incomplete syndrome of Basedow's disease, with osseous metastases (Syndrome de Basedow incomplet chez une malade ayant une petite tumeur thyroidienne avec métastase osseuses). Tixier (L.) & Duval (H.), Bull. et mém. soc. méd. d. hôp. de Par., 1921, **45**, 875-877.

The authors report the case of a woman of 67 years who was much emaciated. Tremor and tachycardia were evident. A small tumor of the left lobe of the thyroid was palpable. In view of the distribution of metastases in the osseous system the thyroid tumor was considered malignant and to be the cause of the symptoms of Basedow's disease.—F. S. H.

Creatin metabolism and the THYROID (Kreatinstoffwechsel und Schilddrüse). Tseke (C.), Monats. f. Kinderh. (Berlin), 1921, **21**, 337-350.

Creatin is found in the urine of normal children of 1½ years. In hypothyroidism creatin fails to be found in urine of children. Of course if the only symptom found in a child is a lack of creatin this is not enough for a diagnosis of hypothyroidism. Nevertheless, it is an important symptom. In hyperfunction of the thyroid in children the urinary creatin is generally increased. Also in Graves' disease the quantity of excreted creatin is high; also in fever, toxicosis and in serious diabetes. As a test for the activity of thyroid preparations the author recommends observation of its influence on the amount of creatin in the urine of children. This must be markedly raised.—J. K.

The influence of THYROPARATHYROIDECTOMY upon blood sugar content and alkali reserve. Underhill (F. P.) & Nellans (C. T.), J. Biol. Chem. (Balt.), 1921, **48**, 557-561.

The removal of the thyroid apparatus from dogs results in a lowered blood sugar content. There seems to be little or no change in the carbon dioxide capacity of the blood up to the onset of tetany. After this period there may be a decided tendency toward a diminished alkali reserve.—F. S. H.

(THYROID) Congenital goiter (Over aangeboren kropgezwellen). van Goor (W. T.), Inaug. Dissertation, Amsterdam, 1921.

Congenital goiter has never been described in the Dutch medical literature. Van Goor has now studied the weight of the thyroids of newly born children in Amsterdam (where goiter is not endemic). The average weight is 1.5 gram. In countries where goiter is endemic the average weight is much higher, even when no congenital goiter is found. In regions with endemic goiter the number of cases of congenital goiter is much larger than elsewhere. In a children's hospital in Berne in 22 years, 53 cases of congenital goiter were observed; in two of the largest hospitals in Amsterdam only 5 cases were seen in the same period. To avoid congenital goiter mothers during pregnancy often go to places which are free from goiter. Local circumstances certainly are of influence, but heredity also plays an important part. In many cases no cause can be detected. The histological structure of the congenital goiter varies widely; a typical picture does not exist. Congenital goiter always takes its origin from the thyroid proper. Goiters of the tongue, struma retrosternalis, etc., are never congenital. The weight of these goiters differ. In one case described it was 58 gm. They often contain cysts. Teratomas of the thyroid have been described. The author proposes the following scheme of classification: I. Thyroid enlarged through hyperaemia—(a) goiter with hyperplasia of the blood vessels. II. Hyperplastic goiters—(b) goiter with hyperplasia of the parenchyma, (1) solid follicles, (2) follicles with colloid, (3) follicles with papillary formation; (c) struma cystica; (d) struma fibrosa. III. Teratoma of the thyroid. The symptoms of these goiters are dyspnoea or asthma neonatorum. The treatment must be surgical; three operations are possible: (1) to cut through the isthmus; (2) exothyreopexia; (3) strumectomy. Tracheotomy or intubation must be emphatically warned against.—J. K.

(THYROID) Classification of goiter: an analysis of one hundred cases. Williams (C.), Am. J. M. Sc. (Phila.), 1921, **161**, 223-228.

This paper attempts the correlation of the clinical histories and pathologic findings in 100 cases. The author further outlines the indications for surgical treatment of goiter. During the time selected

for study this clinic admitted 103 goiters and operated upon 100. The other three presented contra-indication for any surgical interference.—J. F.

Malignant tumors of the THYROID. Part I. Wilson (L. B.), Collected Papers Mayo Clinic, 1920, **12**, 376-385. (Reprinted from Ann. Surg.).

Nine hundred and seventy-one cases of malignant goiter are collected from the literature. The cases occurring in the Mayo Clinic are then reported as a group and analyzed as to clinical course, sex, age, and geographic distribution.—J. F.

(THYROID) A malignant hemangio-endothelioma of the thyroid (Ein malignes Hämangioendotheliom der Schilddrüse). Winnen (P.), Frankfurt. Ztschr. f. Path. (Wiesb.), 1920, **23**, 405-418.

Reports case of 47 year old female with a large goiter of thirty years' standing which suddenly started to enlarge rapidly. Clinically a diagnosis of carcinoma of the thyroid was made. An operation performed and death followed ten days later. At necropsy it was found that the tumor locally had infiltrated the trachael and esophageal walls. There were multiple metastases to the lungs. The author discusses at length the data for considering the tumor an endothelioma, all of which is purely morphological and therefore not absolutely convincing. It is well known that the thyroid tissue tumors offer peculiar difficulties as regards differentiation morphologically into sarcomas, carcinomas and endotheliomas.—D. M.

(THYROID) Comparative study of the frequency of different forms of goiter in Basel and in Bern (Vergleichende Untersuchungen uber die Häufigkeit de verschiedenen Knopfformen in Basil and in Bern). Woelz (E.), Schweiz. med. Wchnschr., 1921, **51**, 625.

These observations are based on the surgical material from the clinics in Basel and Bern. Diffuse goiters (parenchymatous and colloid) were more common in Basel than in Bern, while nodular goiters (struma nodosa) were less common in Basel than in Bern. The relation of diffuse goiter in Basel and Bern is 3:2. This difference may be due to the greater number of operations for Basedow's disease in Basel.—D. M.

Traitement THYROIDIEN de la furonculose. Savini (E.), Prog. Méd. (Paris), 1921, **36**, 178-179.

Having had excellent results with thyroid treatment in a case of furunculosis complicating eczema, Savini systematically treated a series of cases of furunculosis with this drug, giving 2-3 cgm. every other day. The results were notably satisfactory. Nineteen males from 16 to 43 years old and eight females, 19 to 32, were

included in the series. The results were explained as due to two factors: stimulation of the defensive mechanisms and attenuation of the anaphylactic condition created by the infection itself.—R. G. H.

Studies of the chemical composition of the THYROID gland. Zűnz (E.), Arch. intern. de physiol. (Paris), 1921, **16**, 288-306.

This is probably the most extensive tabulation of analyses of the thyroid gland. It is shown that the thyroid of man weighs on the average between 26 and 30 gm. between the ages of 19 and 55 years. The variability, however, is great. The H_2O content also varies within relatively wide limits, but approaches a mean of 75% to 76% for all ages in which the weight of the gland does not pass 60 gm. The average composition remains relatively constant in the adult in spite of large individual variations observed at all ages. There is always found more iodine in the glands obtained from men between 25 and 55 years of age than in glands from men of 19 to 24 years. This average content of iodine in the fresh or dry gland tends to increase with the diminution in weight of the thyroid. The iodine content averaged 0.56 mgm. per gm. of fresh substance from 19 to 44 years; it increased gradually from 0.23 mgm. in heavy glands to 0.68 mgm. in glands of low weight. No particular difference in the iodine content of the two lobes was found.—Chem. Abst., **15**, 2116.

The excitation of surviving UTERUS and intestine by organ extracts and dialysates (especially those of the UTERUS) [Die Erregung des überlebenden Uterus und Darmes durch Organextrakte und diolysate (besonders aus dem Uterus)]. Backman (E. Louis), Arch. f. d. ges. Physiol. (Berlin), 1921, **189**, 261-281.

Dialysates of rabbit uterus contain substances which stimulate rabbit intestine. The action is not antagonized by atrophine and is only slightly strengthened by acetylising. It cannot therefore be due to choline. Over 90% of the observed action is due neither to choline nor to serum compounds. Similarly dialysates, and also aqueous and alcoholic extracts of cow-uterus excite rabbit and guinea pig uterus and rabbit intestine, and 90% to 96% of the action is due to other substances than choline or blood serum compounds. These substances are not destroyed by boiling, are soluble in alcohol, and are not produced by bacterial action nor by autolysis. Intestine and muscle extracts yield substances besides choline with similar properties. Isolated rabbit and guinea pig uterus show varying sensibility to choline. Usually the reaction is much less than that of the intestine. Choline therefore is not of importance for automatic uterus movements.—A. T. C.

(VAGOTONIA) The pathogenesis of bronchial asthma (La patogenia del asma bronquial). Mora Quimper (A.), Cron. Méd. (Lima), 1920, **37**, 164-170.

The investigations of late years concerning the relation of endocrinology and the vegetative nervous system have shown the role that vagotonia plays in such different syndromes as bronchial asthma and spasmodic constipation. The author considers bronchial asthma from this viewpoint and explains it on the basis of the antagonistic action between the vagus and sympathetic fibers.—Author's Abst.

VAGOTONIA (Zur Frage der Vagotonie). Pophal, Deutsche med. Wchnschr. (Berlin), 1921, **47**, 881.

The teachings of Eppinger and Hess prove that the authors do not know the meaning of the word "tonus." Tonus has nothing to do with the nervous system. An absolute antagonism between the sympathetic and parasympathetic systems does not exist. The pharmacological method of Eppinger and Hess, used for the diagnosis of vagotonia, seems to have no value. Frank has stated that perhaps paralysis agitans is a classical vagotonia. He assumes that every muscle has a parasympathetic innervation; but this has never been proven. Frank also believes that perspiring in paralysis agitans is a symptom of vagotonia. This is not true; the sweat glands have, as far as we know, only a sympathetic innervation. The "vagotonia" is a poor hypothesis, built upon unproved statements. (These few lines impress the abstractor as containing more common sense than the complete literature that essays to prove the existence of vagotonia.)—J. K.

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